Jorge Manuel de Carvalho Marques Dourado

HOMO-raising Strategies in Aminocatalysis, from Enamine to Tetraenamine

Dissertação para obtenção do Grau de Mestre em Bioorgânica

Orientador: Maria Manuel Marques, FCT-UNL
Co-orientador: Karl Anker Jørgensen, Aarhus University

Júri:

Presidente: Prof. Doutor(a) Ana Maria Ferreira Costa Lourenço
Arguente(s): Prof. Doutor(a) Maria Manuel Marques
Vogal(ais): Prof. Doutor(a) António Gil de Oliveira Santos

FACULDADE DE CIÊNCIAS E TECNOLOGIA
UNIVERSIDADE NOVA DE LISBOA

Dezembro 2013

LOMBADA

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Abstract

In this Master Thesis two different HOMO-raising strategies in aminocatalysis - enamine activation and tetraenamine activation were studied.

For the tetraenamine activation concept, it was rationalized that the condensation between 2-(cyclohepta-1,3,5-trien-1-yl)acetate and the TMS-protected diraylprolinol ether aminocatalyst would provide the desired tetraenamine intermediate. The novelty of this concept was further explored by the studied of the [4+2]-cycloaddition between the tetraenamine intermediate formed and a series of 3-olefinic oxindoles, benzofuranone and benzothiophenone. The corresponding cycloaddition products were obtained bearing four stereocenters including a spiro-carbon with yields between 51 and 93%.

The reaction also proved to be both diastereo- and enanteoselective with the dr ranging between 86:14 and >95:5 and ee between 50 and 99%.

Furthermore, the isolated cycloadducts were subjected to several transformations including an oxidation reaction under Dess-Martin conditions, which produced a highly substituted cyclohexanone and a selective bromination of the triene system of the cycloadduct which occurred with total regioselective control.

In this project, mechanistic studies were also performed allowing the isolation and/or characterization of a series of intermediates namely the tetraenamine, which allowed a mechanistic proposal that was then supported by computational calculations.

In this Thesis was also explored the well known enamine activation concept. It was intended to perform a Michael reaction between a series of aldehydes and vinyl sulfones catalyzed by a bifunctional H-bond directing aminocatalyst. For this purpose isovaleraldehyde and phenyl acetaldehyde were tested with methyl vinyl sulfone, phenyl vinyl sulfone and trifluoromethy lvinyl sulfone in the presence of either a squaramide based aminocatalyst or a TMS-protected diraylprolinol ether aminocatalyst. Despite the several attempts and modifications of the reaction conditions no reactivity was observed which could be explained by the lack of activation of the Michael acceptor (i.e. the vinyl sulfones). The results obtained suggest that new catalytic systems should be explored in order to perform the conjugate addition of aldehydes to vinyl sulfones.

Resumo

Nesta Tese de Mestrado foram estudadas duas estratégias diferentes de aumento de energia da HOMO em aminocatálise - activação por enamina e activação por tetraenamina.

No que respeita ao conceito de activação por tetraenamina, pensou-se que a condensação entre o 2-(ciclohepta-1,3,5-trien-1-il)acetaldeído com um aminocatalisador do tipo diarilprolinol protegido por um grupo TMS desse origem ao intermediário tetraenamina. A novidade deste conceito foi provada através da ciclo-adição [4+2] entre a tetraenamina obtida e uma série de oxindoles 3-olefinicos, benzofuranona e benzotiofenona, obtendo-se assim o respectivo produto de ciclo-adição possuindo quatro carbonos quirais, sendo um deles spiro, com rendimentos entre os 50 e 90%.

A reacção também demonstrou ser diasterio- e enantiosselectiva com um dr entre 86:14 e >95:5 e um ee entre 50 e 99%.

Após a obtenção dos produtos de ciclo-adição foi possível efectuar algumas transformações nomeadamente, uma oxidação de Dess-Martin que produziu uma ciclo-hexanona com elevado padrão de substituição e efectuou-se ainda a bromination selectiva do sistema triconjugado com total regiocontrolo sobre este processo.

Realizaram-se ainda estudos mecanísticos que permitiram o isolamento e/ou caracterização de uma série de intermediários, entre os quais a tetraenamina, que permitiram determinar o mecanismo da reacção, tendo este sido posteriormente comprovado por estudos computacionais.

Um outro projecto descrito nesta Tese está relacionado com o já bem estabelecido conceito de activação por enamina. Neste projecto pensou-se em realizar um conjunto de reacções de Michael entre uma série de aldeídos e vinil sulfonas, catalisado por um aminocatalisador bifuncional.

O isovaleraldeído e o fenilacetaldeído foram testados com metil vinil sulfona, fenil vinil sulfona e trifluorometil vinil sulfona na presença quer de um aminocatalisador à base de uma squaramida, quer de um aminocatalisador derivado do diarilprolinol. Apesar das várias tentativas e mudanças nas condições reaccionais, não foi observada nenhuma reactividade. Esta observação pode ser devida à falta de activação dos aceitadores de Michael (i.e. vinil sulfonas). A pesquisa de novos sistemas catalíticos poderá dar resposta ao problema.

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List of Abbreviations

[M^+]	molecular ion
^{13}C NMR	Carbon Nuclear Magnetic Ressonance
^{1}H NMR	Proton Nuclear Magnetic Ressonance
Ac	acetyl
Ar	aryl
BA	benzoic acid
BINOL	binaphthol
Bn	benzyl
Boc	*tert*-butyl carbamate
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethyl
DEA	diethylacetamide
DFT	density functional theory
DMA	*N*,*N*-dimethylacetamide
DMAP	dimethylamino pyridine
DMP	Dess-Martin periodane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
E^+	electrophile
Ea	activation energy
ee	enanteomeric excess
equiv.	equivalent
Et	ethyl
EWG	electron withdrawing group
FC	flash chromatography
g	gram
h	hour
HOMO	Highest Occupied Molecular Orbital
Hz	Hertz
***i*-Pr**	isopropil
J	coupling constant
kcal mol^{-1}	kilocalory per mole
LUMO	Lowest Unoccupied Molecular Orbital
m	multiplet
Me-BA	2,4,6-trimethylbenzoic acid
Me	metil
MHz	megaHertz
min	minute
mL	milliLiter
mmol	millimole
Mp	melting point
MS	molecular sieves
Ms	mesyl

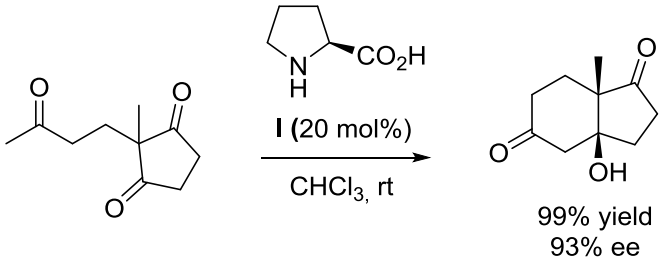
***n*Bu**	*n*-butyl
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Ressonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
***o*-FBA**	*ortho*-fluorobenzoic acid
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
q	quartet
rt	room temperature
s	singlet
S_N1	unimolecular nucleophilic substitution
SOMO	Single Occupied Molecular Orbital
T	temperature
t	triplet
TBDPS	*tert*-butyldiphenylsilyl
***t*Bu**	*tert*-butyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TS	transition state
Ts	tosyl
UPC^2	Ultra Performance Chiral Chromatogrphy
δ	chemical shift

Chapter I - Introduction

I.1 - Organocatalysis

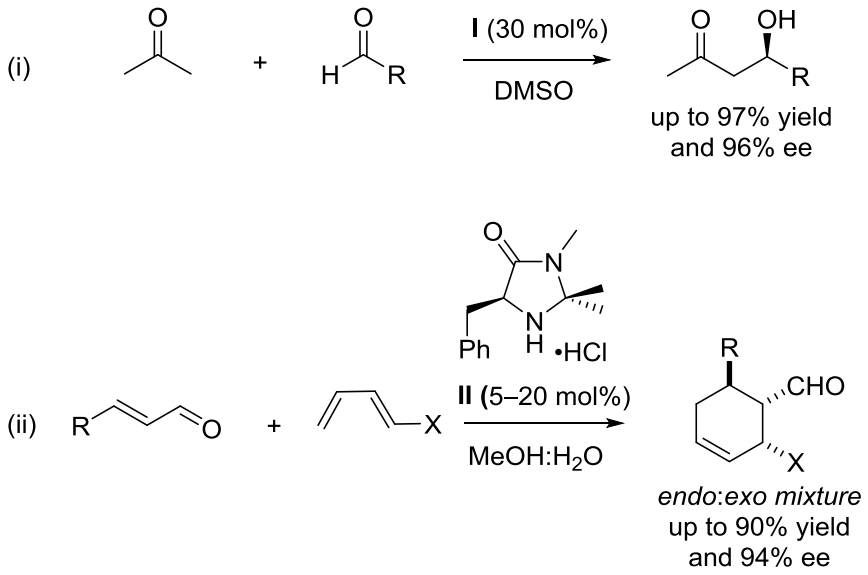
The use of catalysts in chemistry is of great importance and it is an area that has been widely consolidated throughout the years. A textbook definition of a catalyst is that of a specie which increases the rate of a reaction, by decreasing its activation energy (Ea), while it is not consumed in the overall reaction scheme. Furthermore, catalytic processes may also enable chemists to perform reactions that otherwise would not take place and grant great regio-, chemio- and stereocontrol. There are three main areas of catalysis in chemistry namely (i) organometallic catalysis; (ii) biocatalysis; and (iii) organocatalysis.

Despite the sporadic publications that appeared throughout the last century, with the Hajos-Parrish-Wiechert[1] reaction being, probably, the most famous and important example (Scheme 1.1), the field of organocatalysis has only fully emerged in the 2000's.



Scheme 1.1 - Hajos-Parrish-Wiechert intramolecular aldol reaction catalized by proline (**I**).

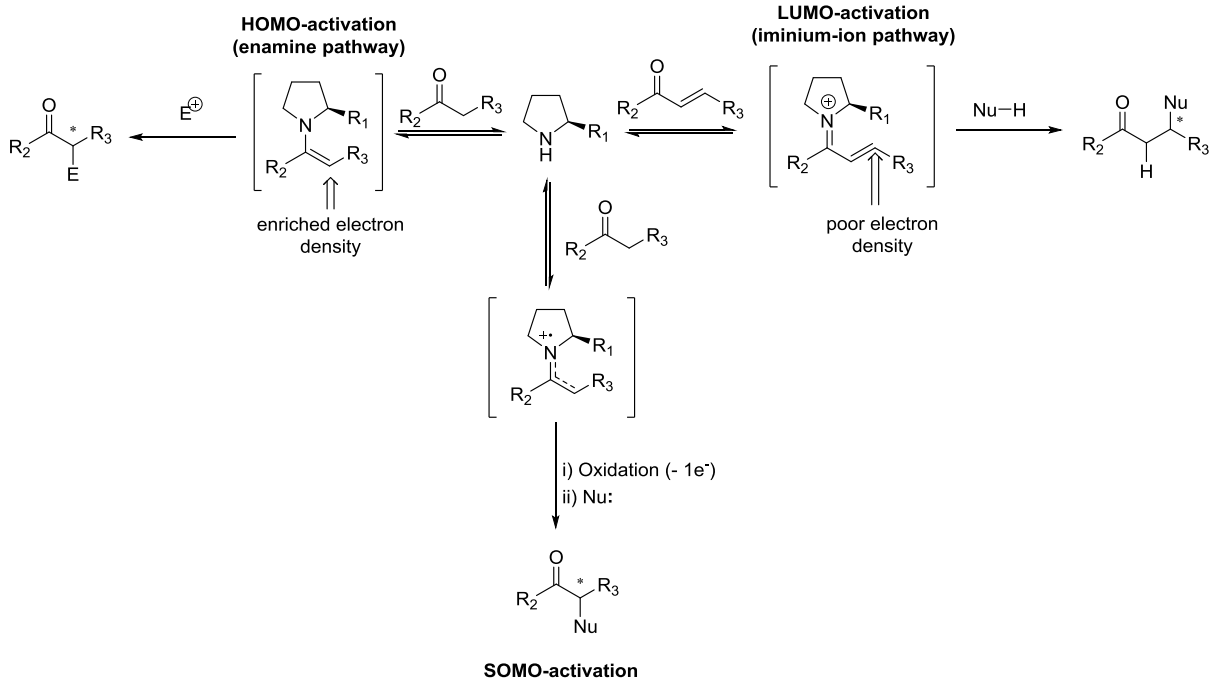
In the year 2000, independent works from Benjamin List *et al*[2] on an enamine mediated aldol reaction catalyzed by proline (**I**) and David W. C. MacMillan *et al*[3] on the iminium-ion mediated Diels-Alder reaction catalyzed by an imidazolidinone (**II**) derivative (Scheme 1.2), made the field of organocatalysis appear.



Scheme 1.2 - Work done by Benjamin List *et al* (i); and by David W. C. MacMillan *et al* (ii).

Once the field of organocatalysis has been publicly established it grew quickly. The advent of organocatalysis brought to chemists the prospect of a complementary mode of catalysis, with potential for savings in cost, time, energy, easier experimental procedures, and reductions in chemical waste. These benefits arise mainly from three factors. First, organic molecules are generally insensitive to oxygen and moisture in the atmosphere as opposed to metals, so there is no need for special reaction vessels, storage containers, experimental techniques or for ultra-dry reagents and solvents. Second, a wide variety of organic reagents such as amino acids, carbohydrates and hydroxy acids are naturally available from biological sources as single enantiomers. Therefore simple organic catalysts are usually

cheap to prepare or buy from chemical suppliers and readily accessible in a wide range of quantities, suitable for small-scale reactions or industrial-scale reactions. Third, small organic molecules are typically non-toxic and environmentally friendly, increasing the safety of catalysis in both biological and chemical research across all research settings, including industry and academic institutions.
Some critics suggest that low turnover numbers of organocatalysts might limit their potential uses for industrial applications, but this point of view is simplistic to say the least. For any large-scale catalytic process, the most important considerations are the cost and safety. Since organocatalysts are often cheaper than metal-based catalysts, organocatalysts can be used in larger quantities than their metal-based counterparts for the same price. Moreover, it is widely recognized that the removal of toxic catalyst-related impurities from waste streams can often have a larger financial impact than the turnover number of the catalyst. As said before, organocatalysts are typically less toxic than the metal-based ones, so they can be tolerated in large extent in waste streams and are more easily removed, again mitigating the cost of high catalyst loadings[4].
The exploration of new catalytic activation concepts is the backbone of modern synthetic organic chemistry. In the last decade asymmetric aminocatalysis has played an important role in this field using strategies of HOMO- (enamine)[5], LUMO- (iminium-ion)[6] and SOMO-activation[7] to activate carbonyl compounds such as aldehydes and ketones (Scheme 1.3). Aminocatalysis is one of the fields in organocatalysis which makes use of chiral primary or secondary amines to activate carbonyl compounds such as aldehydes or ketones.



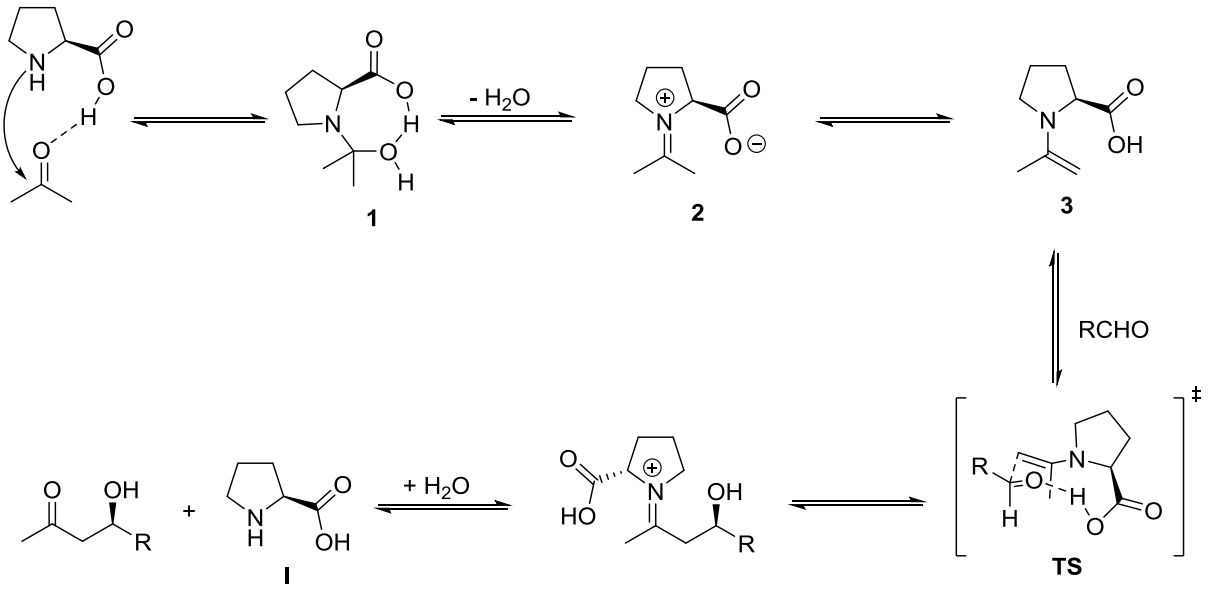
Scheme 1.3 - Classical activation concepts in aminocatalysis.

When the field of aminocatalysis was merged with the vinylogy principle[8] chemists were able to transfer the reactivity to extended π-systems obtaining products bearing new stereocenters located several bonds away from the face differentiating element of the catalyst without loss of stereoselectivity (i.e. high ee's). Such modes of activation came to be known as dienamine, vinylogous iminium-ion, trienamine and cross-trienamine[9, 10]. In the next sections each one of these new activation concepts will be briefly discussed. No special attention will be given to SOMO-activation as it was not used in the work presented in this Thesis.

I.2 - HOMO-raising strategies

I.2.1 - Enamine mediated catalysis

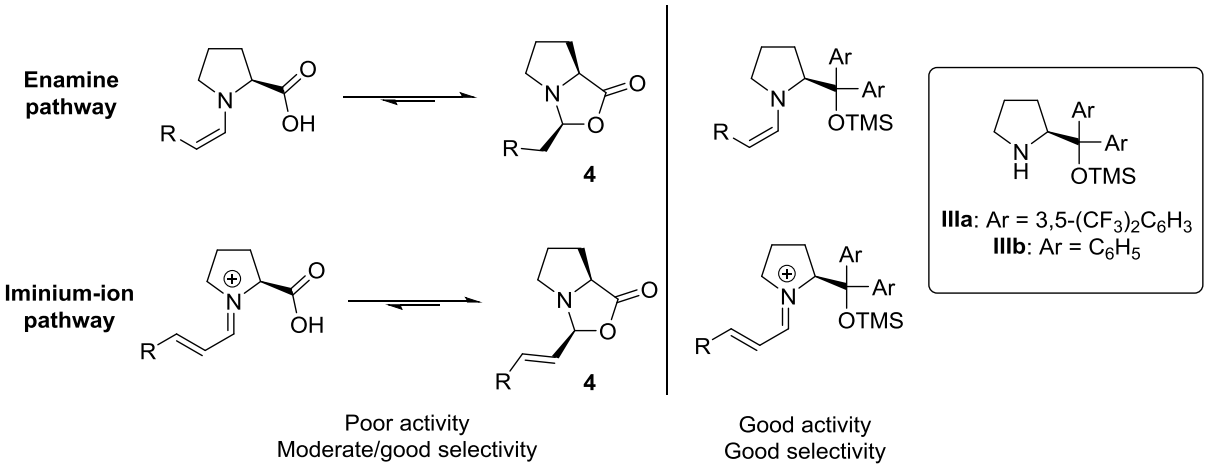
The first catalyst used for enamine mediated catalysis was proline (**I**) and was widely used for asymmetric aldol reactions being its mechanism of reaction similar to the one of aldolase enzymes. This simple amino acid is able to catalyze intermolecular aldol reactions giving moderate to good ee's depending on the nature of the substituents on the aldehyde molecule. The mechanism of the intermolecular aldol reaction catalyzed by **I** is shown is Scheme 1.4.



Scheme 1.4 - Proposed mechanism for the proline-catalyzed intermolecular aldol reaction.

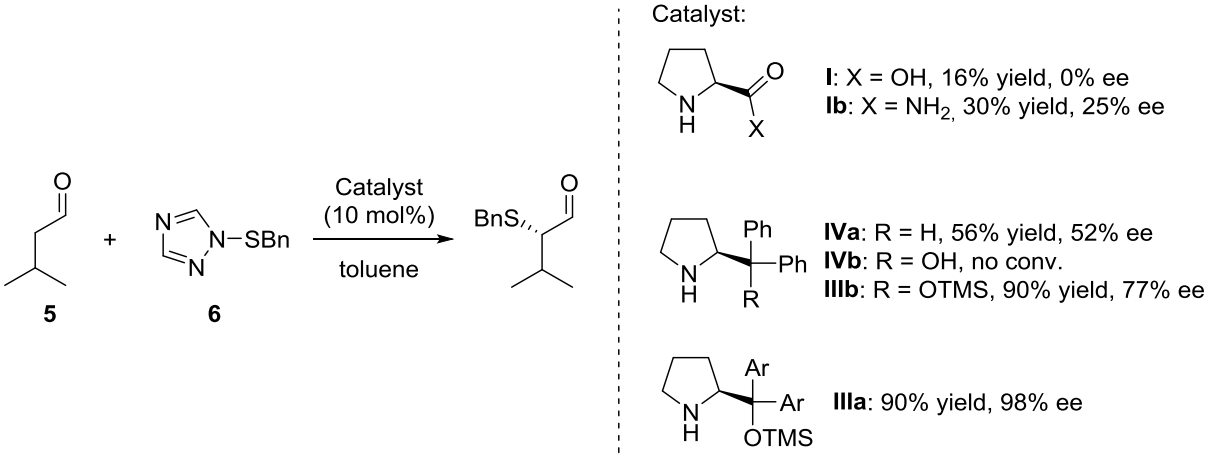
The high levels of reactivity and selectivity induced by proline (**I**) stem from the simultaneous exploitation of both amino acid functionalities. Primarily, the nucleophilicity associated with the nitrogen atom of the pyrrolidine ring facilitates the condensation with a carbonyl substrate producing intermediate **1** which immediately collapses to the iminium-ion **2**. This species, even though, susceptible to a nucleophilic attack tends to undergo an α-deprotonation forming the enamine **3**. This nucleophilic molecule can then react with an aldehyde which is directed through H-bonding by the acid moiety of the enamine thus yielding the observed enanteoselectivity. This H-bond interaction provides both preorganization of the substrates in the transition state **TS** and stabilization of the forming alkoxyde[11]. This mechanism is closely related to the one that occurs in enzymatic processes carried out by aldolases and has been widely supported by experimental and theoretical investigations[12].

The major problem observed with proline catalyzed reactions is the formation of a parasitic oxazolidine species (**4**) which may lead to the entrapment of the catalyst (Scheme 1.5) in 2005 Jørgensen's group[13] rationalized that the simple protection of the hydroxyl moiety by a TMS group allied to the presence of two aromatic units would increase both the activity and selectivity of the catalyst in a wide range of reactions based on both HOMO- and LUMO-activation concepts.



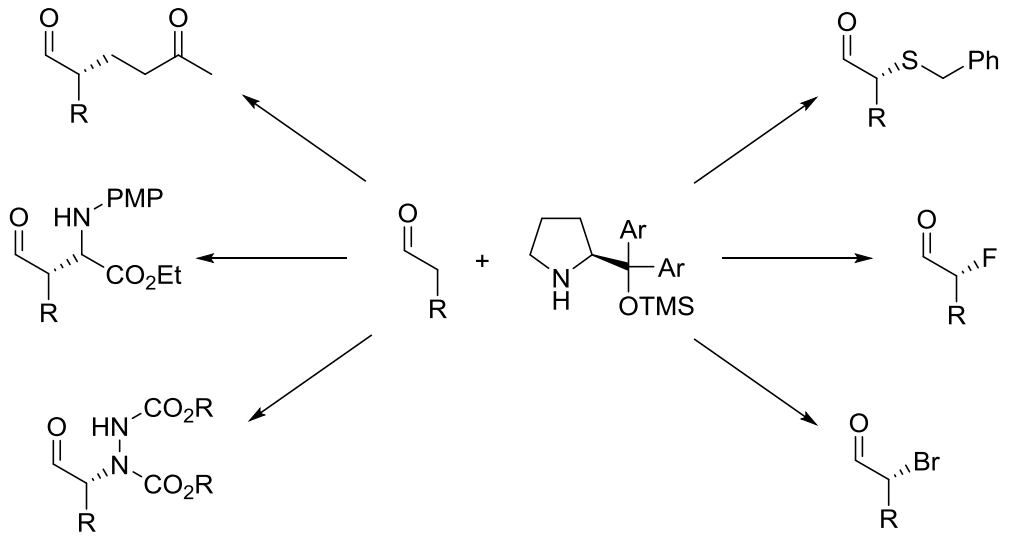
Scheme 1.5 - Comparison between the activity and selectivity of proline (**I**) and a TMS-protected diarylprolinol (**III**).

These new catalysts **IIIa** and **IIIb** were first tested in the α-sulfenylation of aldehydes performed by Jørgensen's group[14]. As a proof of concept a series of catalysts were tested in a model reaction between isovaleraldehyde (**5**) and 1-(benzylthio)-1,2,4-triazole (**6**) (Scheme 1.6) and only catalyst **IIIa** gave satisfactory results (90% yield, 98% ee).



Scheme 1.6 - Scope of catalysts for the α-sulfenylation of isovaleraldehyde **5.**

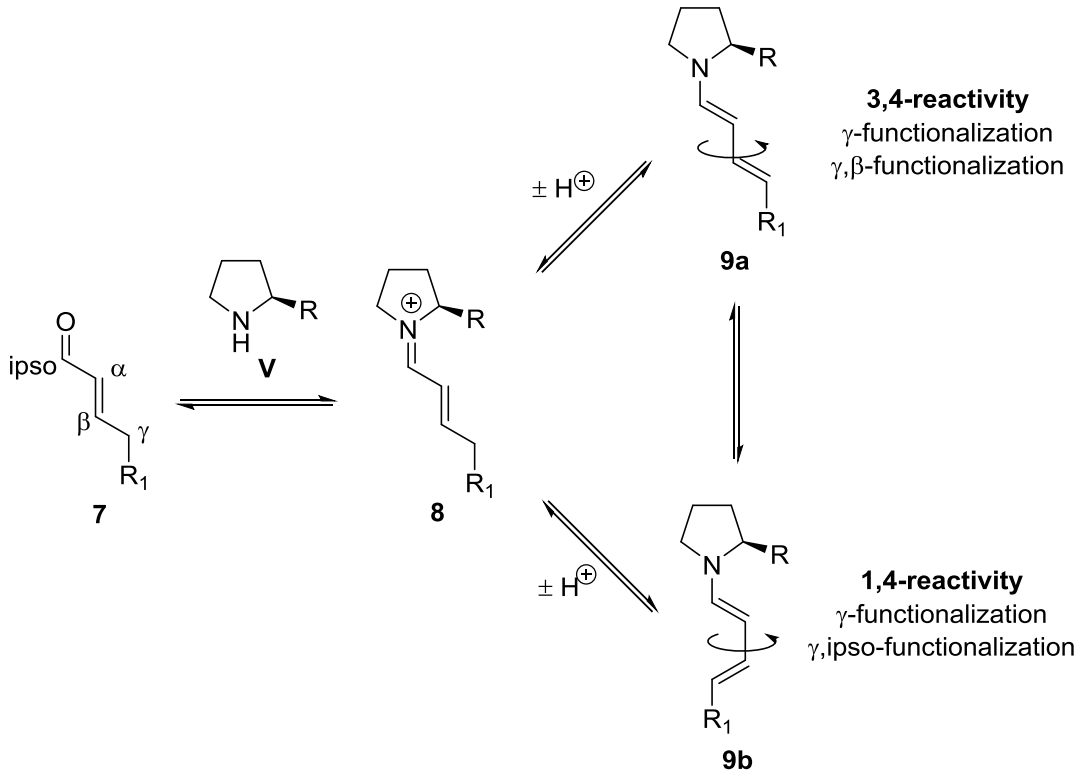
With the development and study of new general catalysts research groups around the world soon found new reactions for enamine mediated chemistry like α-sulfenylations, -halogenations, -aminations, Michael additions, and Mannich reactions of carbonyl compounds (Scheme 1.7)[11, 13].



Scheme 1.7 - Enamine mediated α-functionalizations of aldehydes.

I.2.2 - Dienamine mediated catalysis

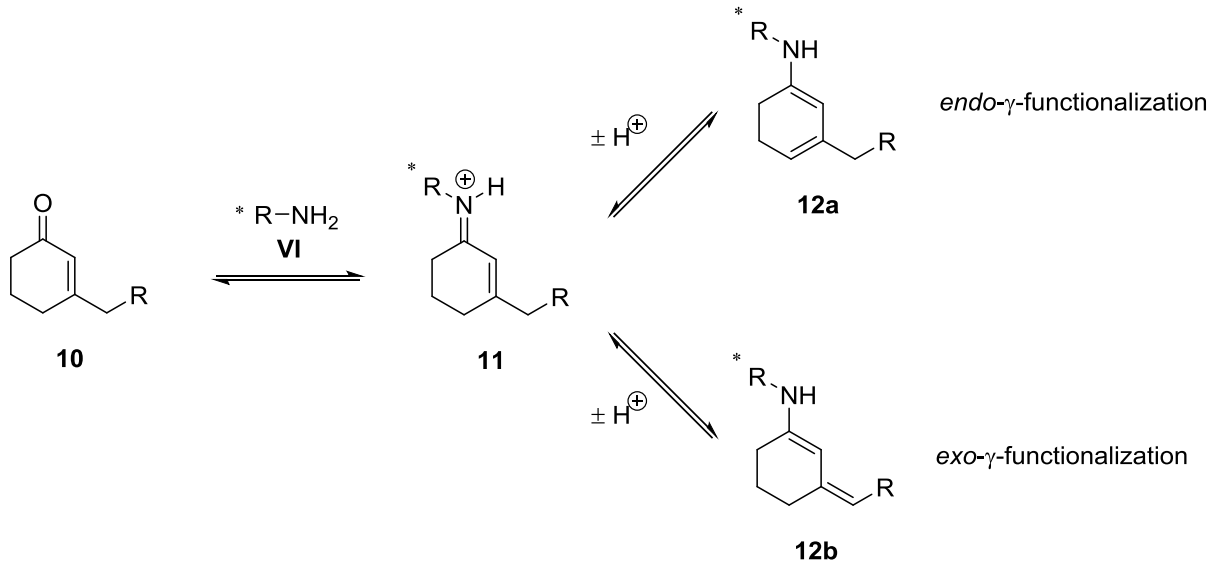
The dienamine **9** can be obtained from α,β-unsaturated aldehydes (**7**) and an aminocatalyst **V**. Upon condensation between these two starting materials the resultant iminium-ion **8** can undergo a deprotonation step if γ-hydrogen atoms are present affording **9** (Scheme 1.8).



Scheme 1.8 - Remote functionalizations via dienamine intermediates.

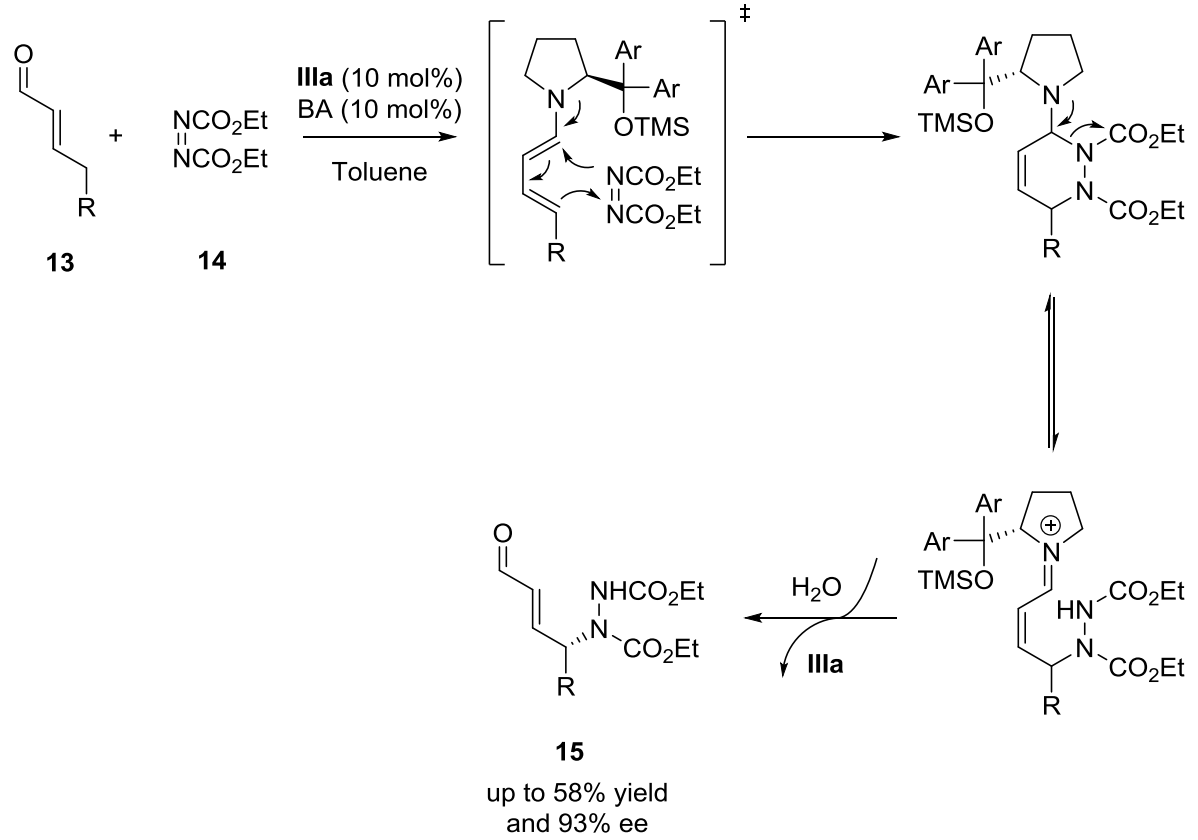
When dienamine **9** is considered three different reaction pathways may take place. First there's the α- or α,ipso-functionalization which are both basically enamine activation methods and therefore have already been discussed in the previous section. The other two types of reactivity are illustrated in Scheme 1.8 and are of more interest to the chemical community. With this dienamine intermediates (**9**), one can observe 1,4-reactivity, by a [4+2]-cycloaddition pathway occurring via the intermediate

9b or 3,4-reactivity causing a γ- or γ,β-functionalyzed product via the intermediate **9a**.
Different types of remote functionalizations via dienamine intermediates are also possible when cyclic α,β-unsaturated ketones (enones) **10** are used (Scheme 1.9). The dienamine intermediate **12** can then be obtained upon condensation of the desired enone with a primary amine **VI**. Depending on the structure of the enone one can observe different reactivities such as *endo*-γ-functionalization or *exo*- γ-functionalization.



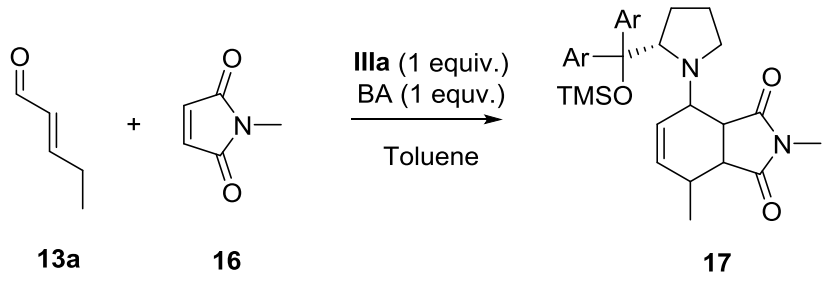
Scheme 1.9 - Remote functionalizations via enone-derived dienamine intermediates.

As evident from the above description, the main challenges related to dienamine strategies, and other remote functionalizations which will be discussed later on, are to control the regioselectivity of the reaction. Furthermore, stereocontrol of the newly introduced stereogenic center(s), located at least five bonds away from the stereodifferentiating element of the catalyst, is another important challenge that must be considered. This issue can be even more demanding when the new stereogenic center is introduced on the electrophilic counterpart. For these purposes, the proper choice of aminocatalyst and reaction conditions is crucial, as the aminocatalyst not only provides the necessary activation, via the HOMO-raising principle, but also offers the required facial discrimination necessary in the stereoselective transformation. In this context it should be noted that the stereochemical outcome of most of the dienamine-mediated reactions is governed by the steric shielding principle with the silyl-protected diarylprolinols being the most commonly group of catalysts used. Recently, the employment of H-bond directing bifunctional catalysts proved very useful, opening new directions in the field[10].
Early investigations by Jørgensen's group[15] highlighted the promising synthetic potential of dienamine mediated catalysis to provide a general synthetic technology for designing direct vinylogous reactions. In their work a series of α,β-unsaturated aldehydes **13** reacted with azadicarboxilate **14** in the presence of the aminocatalyst **IIIa** giving the γ-amination product **15** (Scheme 1.10).



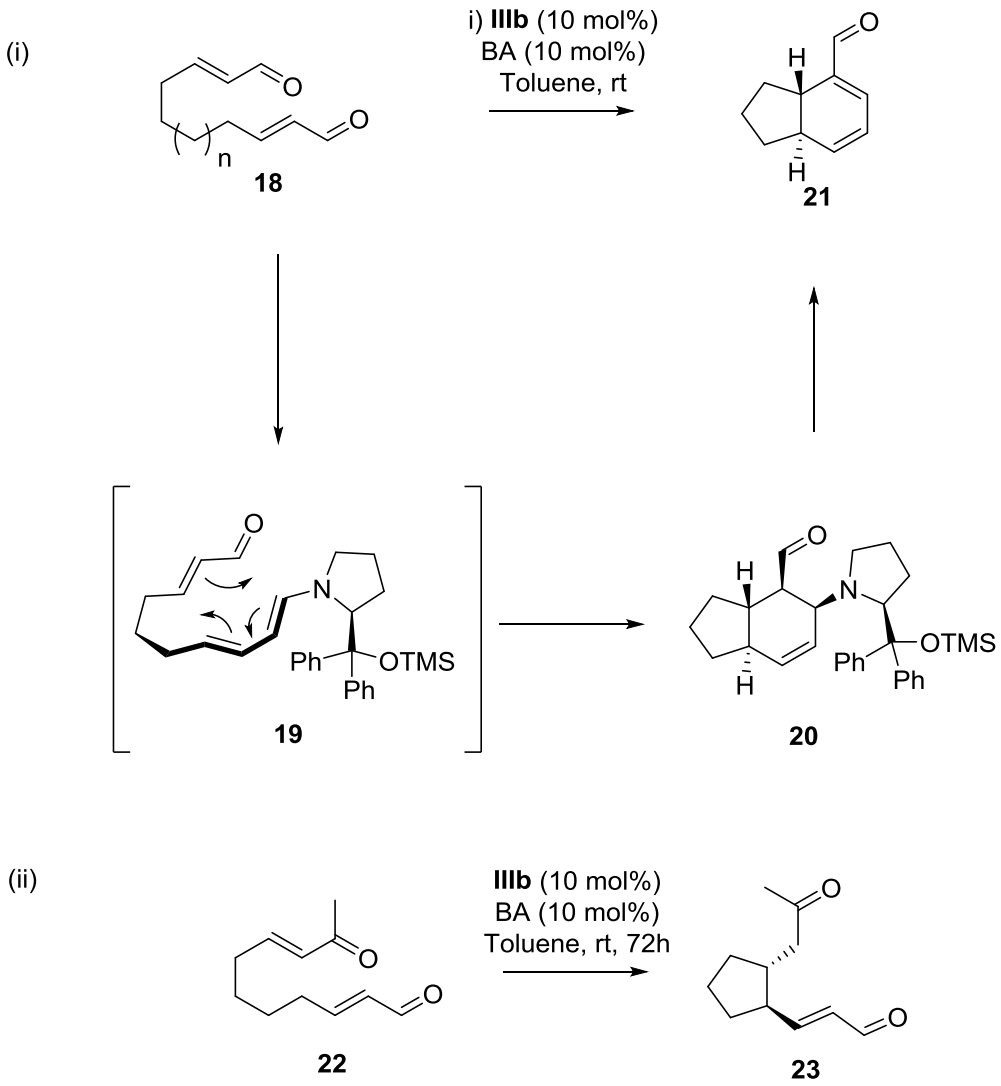
Scheme 1.10 - γ-amination of α,β-unsaturated aldehydes **13** via dienamine intermediates.

In this work, the authors proposed a [4+2]-cycloaddition pathway which not only accounts for the stereochemical outcome but was also confirmed by an independent experiment carried by the authors where they reacted 2-pentenal **13a** and *N*-methylmaleimide **16** obtaining the cycloadduct **17** (Scheme 1.11)[15].



Scheme 1.11 - Entrapment of the catalyst by a carbon-based dienophile.

This showed a particular challenge in dienamine catalysis which is the catalyst turnover, especially in the case of carbon-based dienophiles. Interesting solutions to this problem appeared independently from the groups of Hong[16] and Christmann[17]. The authors demonstrated the possibility of an eliminative release of the catalyst which proves to be a quite general process for various linear and β-branched enals. The work from Christmann *et al* referenced above also gave very important insights into the dienamine chemistry (Scheme 1.12).



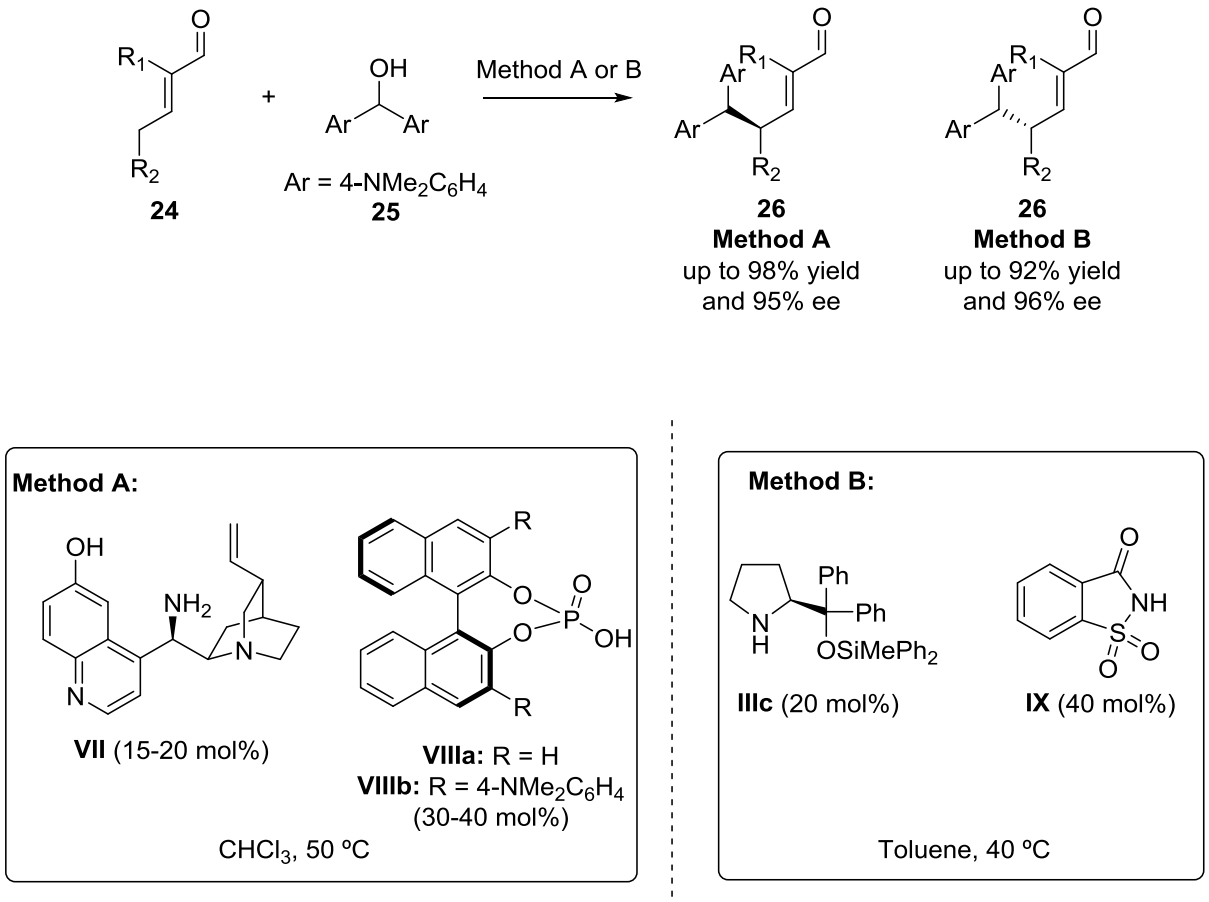
Scheme 1.12 - (i) The intermolecular Diels-Alder reaction of dienals under dienamine activation. (ii) The first example of vinylogous nucleophilic addition.

In this reaction if different substrates are used, different reaction pathways are observed. In eq. (i) of Scheme 1.12 one of the aldehyde moieties in dienal **18** upon condensation with the aminocatalyst **IIIb** form a dienamine species (**19**) which can undergo a Diels-Alder reaction type with the dienamine moiety acting as the electron rich diene and the remaining α,β-unsaturated aldehyde part as the electron poor dienophile. The resulting product **20** can then eliminate the catalyst affording compound **21**. The stereochemical outcome of this reaction is in accordance to what has been described in Jørgensen's paper[15] as the efficient shielding of the chiral fragment of catalyst **IIIb** exposes the unshield face of the π-system in **19** to an *endo* approach.

Changing the aldehyde group to a ketone leads to a completely different reactivity (eq. (ii), Scheme 1.12). Since the catalyst isn't able to condense with the ketone moiety of substrate **22** a vinylogous Michael addition takes place via a dienamine intermediate affording compound **23**.

Soon after the exploration of 1,4-reactivities with dienamine intermediates, direct γ-functionalizations became the main focus of this organocatalytic procedure. The major problem to be addressed would be the regioselectivity of the reaction since the α-functionalization would be a more likely pathway.

In 2010 Melchiorre's group reported the first example of γ-alkylation of α-substituted enals (Scheme 1.13)[18].



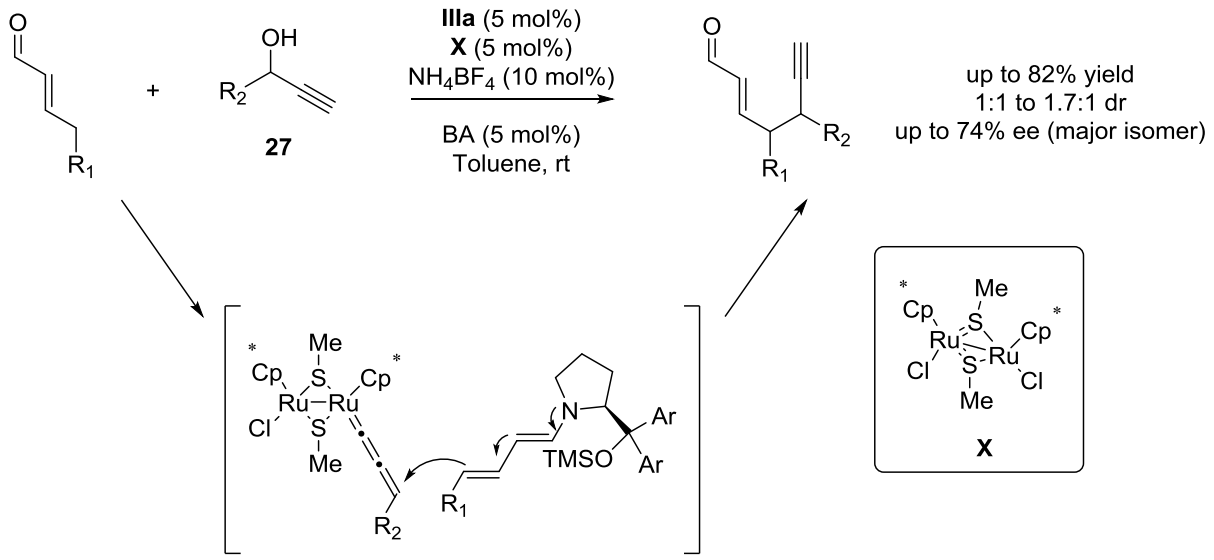
Scheme 1.13 - γ-alkylation of α-substituted enals using two catalytic systems.

In this work the authors used 6'-hydroxy-9-amino quinidine (**VII**) as catalyst to perform the asymmetric S_N1-type γ-alkylation of an α-substituted linear α,β-unsaturated aldehyde (**24**) with bis(4-dimethylaminophenyl) methanol (**25**), which can easily form *in situ* a highly stabilized benzhydryl carbocation under acidic conditions. This reaction was accomplished by integrating the dienamine- and Brønsted acid-catalysis simultaneously.

The use of a chiral BINOL-derived phosphoric acid co-catalyst (**VIII**) was crucial for obtaining high stereoselectivities (Method A, Scheme 1.13). The absolute configuration of both aminocatalyst and co-catalyst had a major impact on the obtained results and only a matched pair resulted in synergic and effective cooperation. The α-substitution on the aldehyde seems to also play an important role in the regioselectivity of the reaction as it contributes to the de-activation of this position by steric effects.

A drawback of this methodology relates to the use of a relatively expensive catalytic system and high catalyst loadings. However, further work from the same group provided a cheaper catalytic system for this reaction by using a diraylprolinol catalyst (**IIIc**) in the presence of a saccharin (**IX**) (Method B, Scheme 1.13)[19].

Recently, Nishibayashi's group proposed an interesting alkylation protocol based upon the synergistic action of a metal- and organo-catalyst. The diruthenium complex **X** in combination with the dirayl prolinol silyl ether **IIIa** promoted the γ-site selective alkylation of linear enals with propargylic alcohols **27**. Despite the poor diastereo- and enanteoselectivities described, this example suggests that cooperative catalytic systems may open new directions for reaction design in dienamine catalysis (Scheme 1.14)[20].

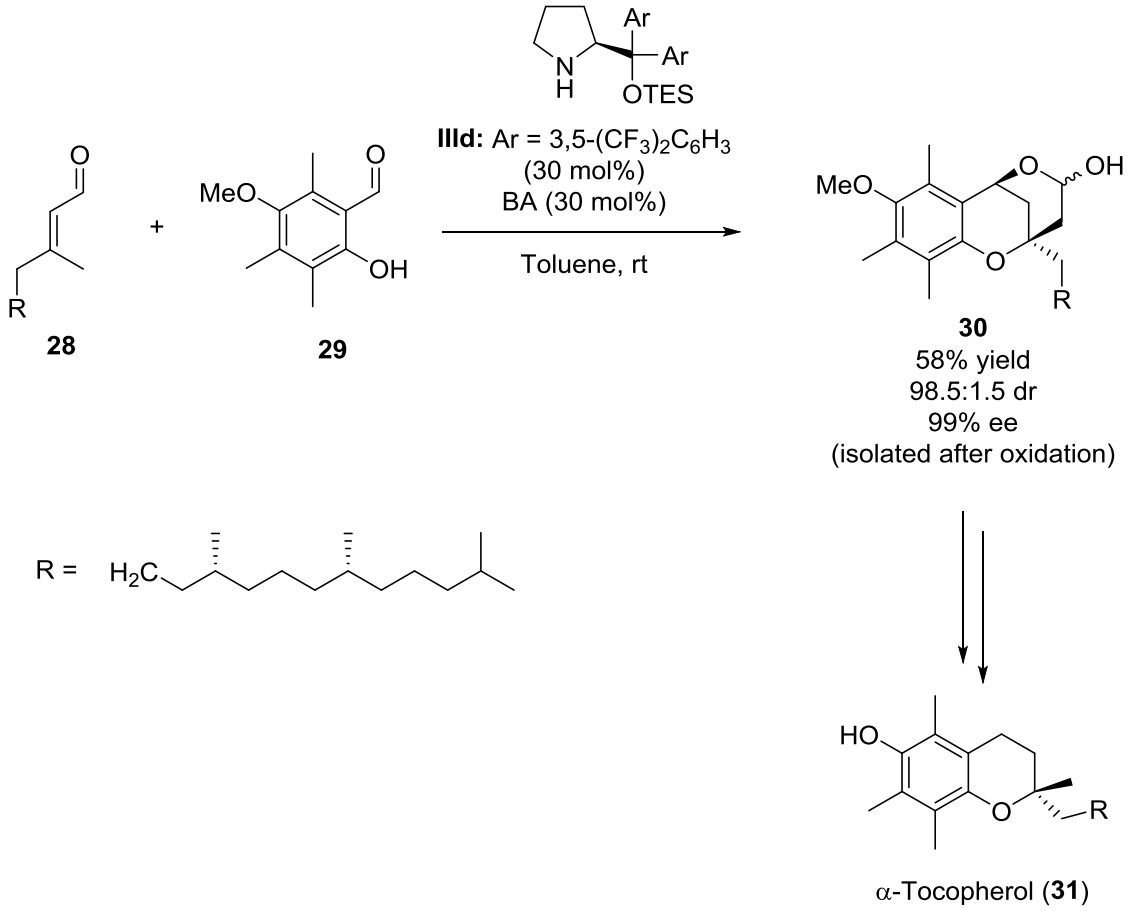


Scheme 1.14 - Nishibayashi's γ-alkylation protocol using propargylic alcohols **27.**

Simple γ-functionalization of dienamines leads to the formation of iminium-ion intermediates which can easily undergo 1,4-addition. For this reason, γ-functionalization of dienamines are frequently followed by subsequent Michael additions, resulting in the γ,β-functionalization of enals.

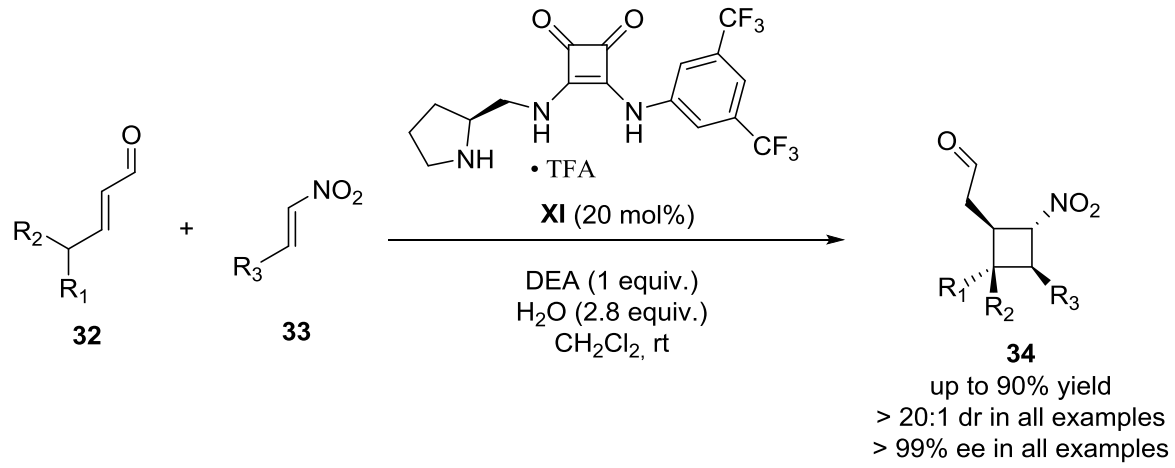
An example of such reactivity was presented by Woggon *et al.*[21] in their total synthesis of α-Tocopherol **31** (Scheme 1.15).

In the key step of this synthesis the authors utilized an aminocatalytic vinylogous aldol reaction followed by cyclization via an oxa-Michael addition. The stereochemistry observed in the product is caused by the sterically demanding triethylsilyl-protected diraylprolinol catalyst **IIId**. Even though there were stereogenic centers present in the side chain of enal **28**, the reaction was fully controlled by the chirality of the catalyst which produced the tricycle **30** with high diastereoselectivity as a single enantiomer (99% ee).



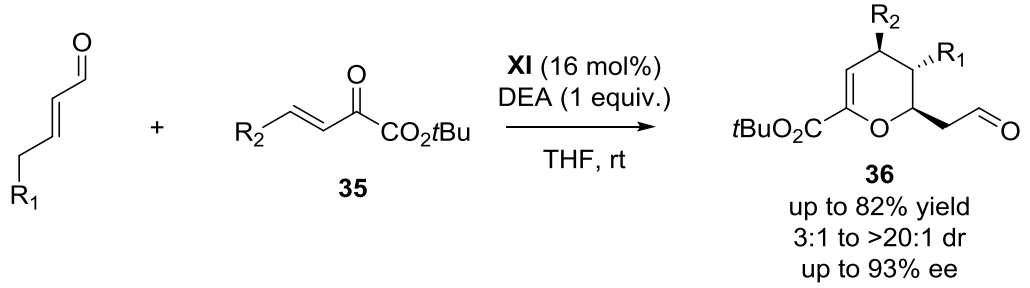
Scheme 1.15 - Application of an aminocatalytic γ,β-functionalization in the total synthesis of α-Tocopherol (**31**).

As mentioned above, regioselectivity in the products obtained via a dienamine intermediate constitutes the biggest challenge in this activation concept with the use of complex and expensive catalytic systems being the answer to this problem. However, recent work from Jørgensen's group introduced a new strategy which could greatly increase the synthetic power of dienamine activation. The main idea was to design a bifunctional secondary amine-thiourea catalyst, which combines the H-bond-directing activation[22] of the electrophile substrate with the dienamine activation of linear unsaturated aldehyde. The simultaneous activation of the two reacting partners would position them in a productive three-dimensional molecular assembly in the TS of the reaction.
This could lead to higher levels of both reactivity and stereo- and regioselectivity. Pursuing this activation prospect Jørgensen's group recently design the bifunctional catalyst **XI**, a chiral secondary amine adorned with a squaramide motif, a well recognized H-bond donor unit[23, 24].
This new catalyst was put to test with the [2+2]-cycloaddition of linear enals **32** with nitroolefins **33** affording the corresponding cyclobutane **34** in high yields and excellent diastereo- and enanteoselectivities (Scheme 1.16)[25].



Scheme 1.16 - [2+2]-cycloaddition of linear enals to nitroolefins catalyzed by a squaramide-based catalyst.

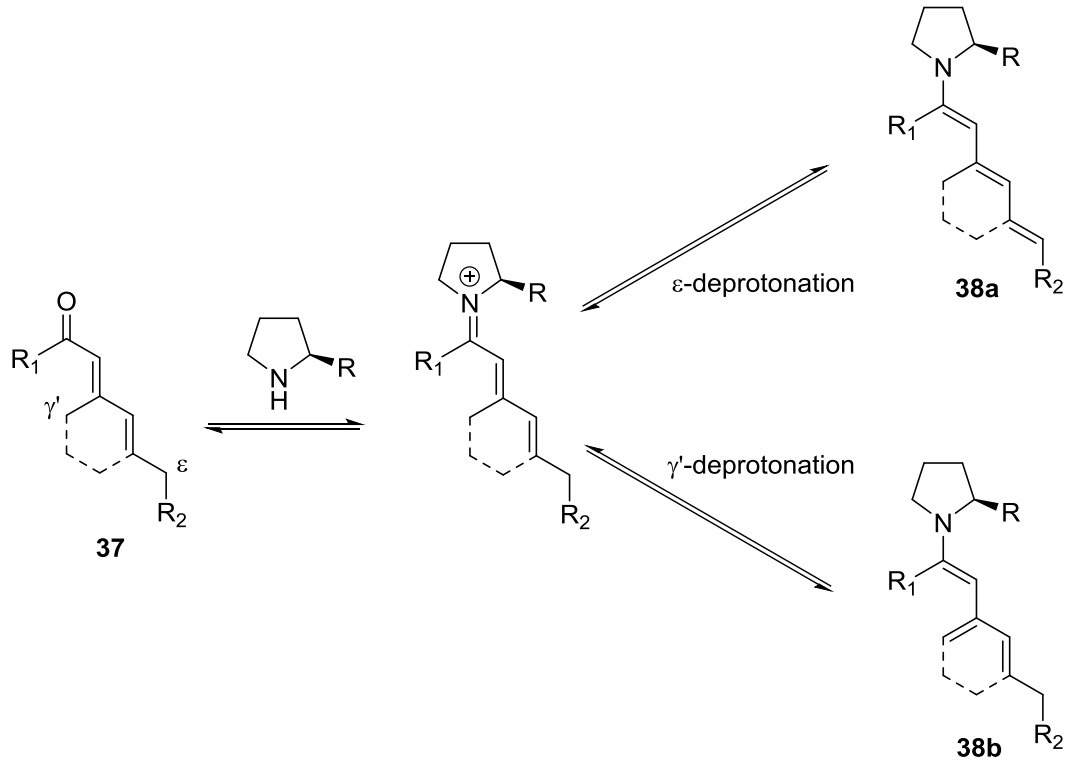
In this kind of catalysis it is noted that the stereochemical outcome arises not from steric effects but from the H-bond directing properties of the catalyst which causes the electrophile to approach the dienamine from the same side as the H-bond donor unit of the catalyst[24].
Another example of H-bond directing aminocatalysis is presented by the same group and involves an inverse-electron-demand hetero-Diels-Alder reaction[26]. In this work Jørgensen *et al.* utilized 2-oxoalk-3-enoates **35** as heterodienes which led to the regio- and stereoselective synthesis of dihydropyran derivatives **36** with three contiguous stereogenic centers (Scheme 1.17). According to the authors, the presence of an aromatic or heteroaromatic substituent in the γ-position (R_1) of the starting enals was crucial for obtaining the desired reactivity.



Scheme 1.17 - H-bond-directing dienamine catalysis in the inverse-electron-demand hetero-Diels-Alder reaction.

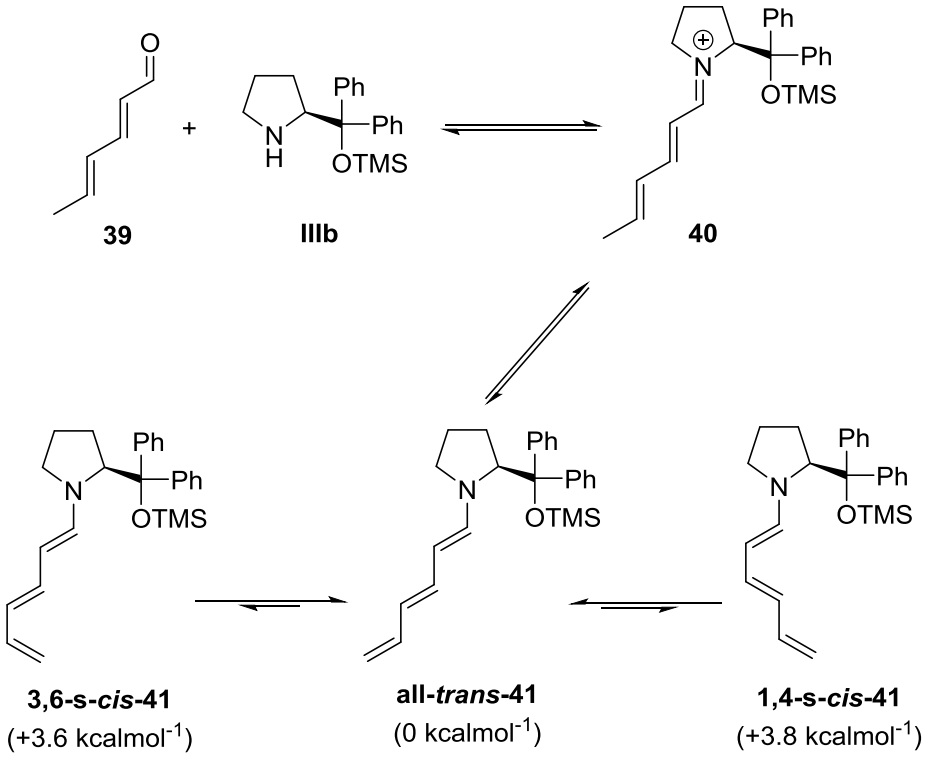
I.2.2 - Trienamine and cross-trienamine mediated catalysis

The success of dienamine activation and its ability to promote highly stereoselective remote functionalizations led to the development of a series of logical, yet intriguing, achievements in aminocatalysis. Recent findings have demonstrated that the HOMO-raising electronic effect can be further propagated within poly-conjugated enals and enones **37**, thus producing trienamine (**38a**) or cross-trienamine (**38b**) intermediates *in situ* (Scheme 1.18).



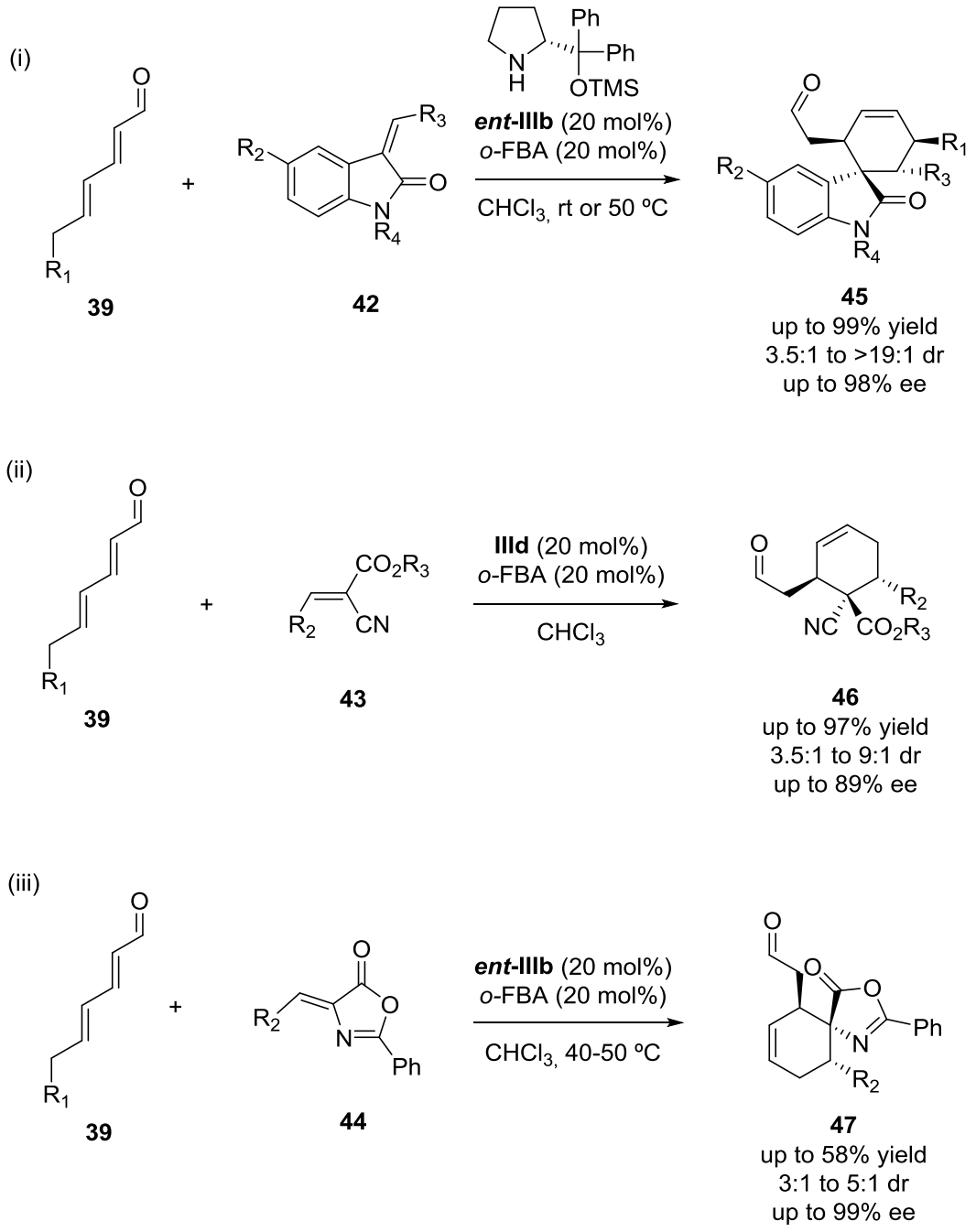
Scheme 1.18 - Trienamine and cross-trienamine intermediates.

The simple logical extension to the use of substrates of greater conjugation gives rise to a range of reactivities and activation modes. Not only do these developments expand the scope of aminocatalytic remote functionalization strategies, but more importantly, they allow the chirality relay to be achieved over greater distances (up to seven bonds) from the face differentiating element of the catalyst.
The viability of the trienamine activation concept was established in a collaborative work between the research groups of Chen and Jørgensen[27]. In this work, condensation of the TMS-protected diarylprolinol ether (**IIIb**) with 2,4-heptadienal **39** led to the transient formation the iminium-ion **40**, which rapidly equilibrates with its tautomer - the trienamine intermediate all-*trans* **41**.
The all-*trans* trienamine **41** was computed as the conformer lowest in energy, while two other possible isomers were located in the calculations, the 1,4-s-*cis*-**41** (3.8 kcal mol^{-1} higher in energy) and the 3,6-s-*cis*-**41** (3.6 kcal mol^{-1} higher in energy) (Scheme 1.19). Furthermore, this work also showed that the rotation barrier to access 3,6-s-*cis*-**41** confrmation was calculated to be 1.8 kcal mol^{-1} lower than the one needed to obtain the 1,4-s-*cis***41**. This fact arises from unfavourable sterical interactions from the bulky chiral element of the aminocatalys which destabilizes this conformation.



Scheme 1.19 - The calculated relative energies of the trienamine conformations.

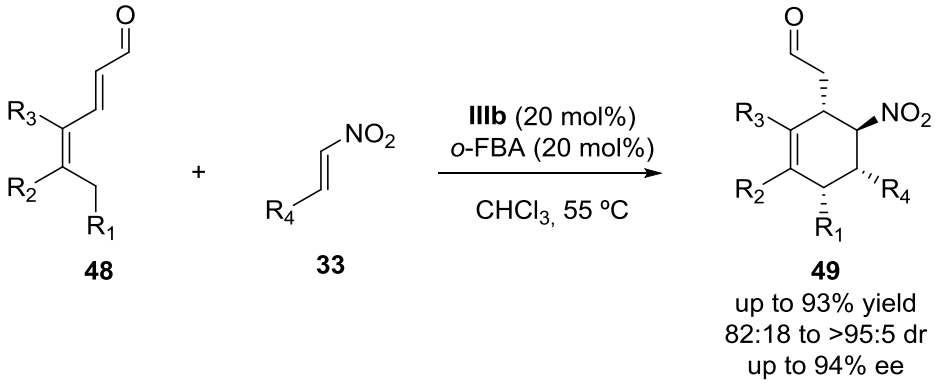
The diene moiety within the 3,6-s-*cis*-**41** was readily submitted to Diels-Alder reaction with different dienophiles, such as olefinic oxindoles **42**[27], or olefinic cyanoacetates **43**[27] and olefinic azlactones **44** (eq.'s (i), (ii) and (iii), respectively, from Scheme 1.20)[28].
This work showed that, despite the long distance between the face differentiating element of the catalyst and the newly formed stereocenters, the reactions proceeded with excellent enanteoselectivities and moderate to excellent diastereoselectivities favoring the *endo*-product. Notably, by employing this strategy a simultaneous functionalization of the ε- and β-positions of dienal **39** is accomplished with high stereocontrol.



Scheme 1.20 - Asymmetric endo-selective Diels-Alder reaction of 2,4-dienals **39** with: (i) olefinic oxindoles **42**; (ii) olefinic cyanoacetates **43**; and (iii) olefinic azlactones **44.**

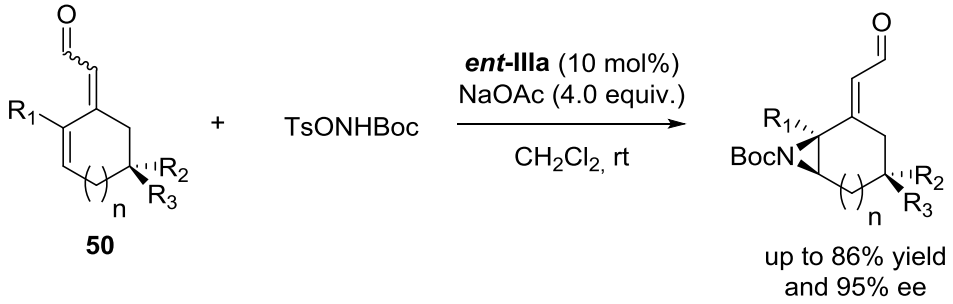
When other known dienophiles, such as nitroolefins **33**, were used with simple dienals no product formation was observed under similar reaction conditions. However, introduction of electron donating groups in various positions of the dienal allowed the desired Diels-Alder reaction to take place with other dienophiles (Scheme 1.21)[29].

The observed increased reactivity was rationalized by the higher electron density of the diene fragment induced by the introduction of the substituents. Intriguingly the nitroolefins gave the *exo*-product as opposed to the above mentioned reactions (Scheme 1.20) this fact was explained by the authors by electrostatic repulsion between the nitro group and the catalyst-bound trienamine.



Scheme 1.21 - Asymmetric *exo*-selective Diels-Alder reaction.

In 2013 Jørgensen's group showed the utility of trienamine mediated catalysis for the remote aziridination of 2,4-dienals[30]. In this work, the authors reacted a series of cyclic 2,4-dienals **50** with TsONHBoc and observed the δ,γ-functionalization of the starting aldehyde (Scheme 1.22).

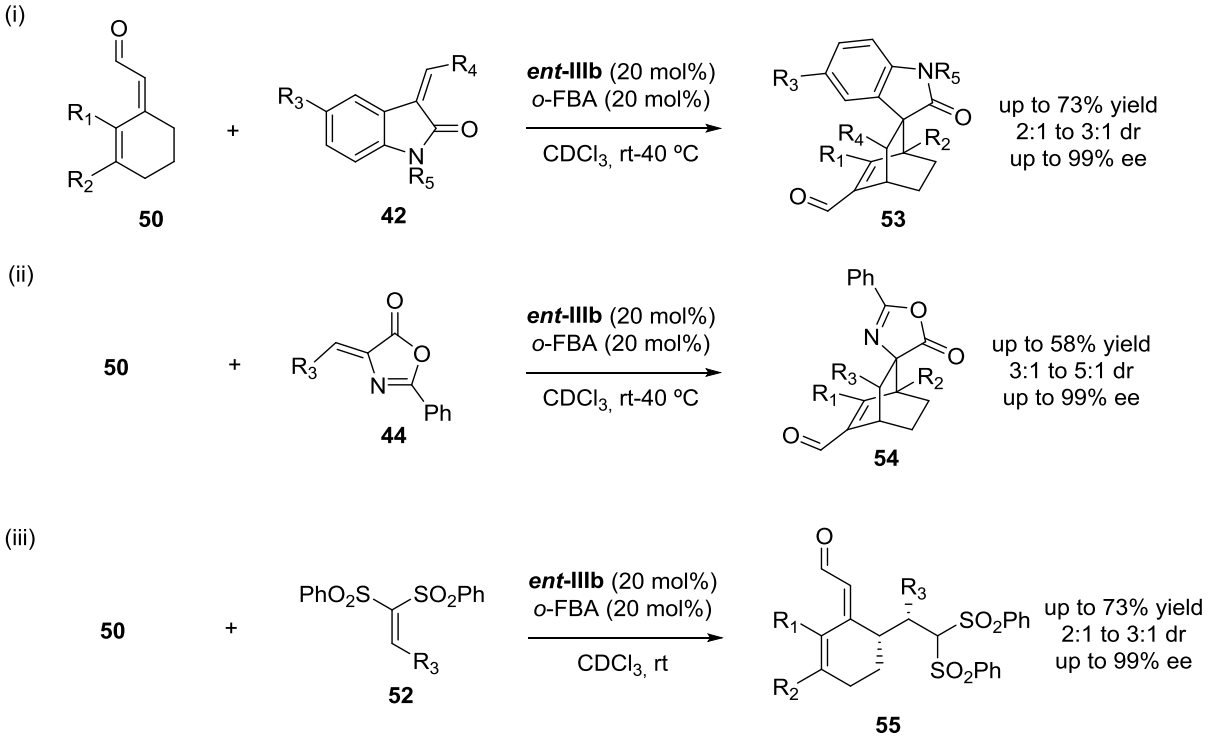


Scheme 1.22 - Remote aziridinaion of cyclic 2,4-dienals **50**.

Curiously the presence of a substituent in the γ-position of dienal **50** was crucial for the reactivity as the use of unsubstituted or linear dienals gave no aziridination product. It is also noteworthy that the dienals derived from both *R*- and *S*-carvones performed very well in this reaction and did not disturb the catalyst activity.

As an attempt to directly produce a 3,6-s-*cis*-trienamine Jørgensen's group decided to use a cyclic dienal **50** and observe its reactivity upon condensation with an aminocatalyst. Interestingly, the condensation product was a cross-trienamine **38b**.

Inspired by the results obtained with the linear trienamine system (Scheme 1.20) Jørgensen *et al*[31] decided to study the reactivity of this new cross-trienamine with a series of Michael acceptors such as olefinic oxindoles **42**, olefinic azlactones **44** and vinyl bis-sulfones **51** (Scheme 1.23) The cross-trienamine also showed good reactivity. Despite the low dr's observed the products main diastereomer was obtained with excellent ee (up to 99%) regardless of the Michael acceptor used.

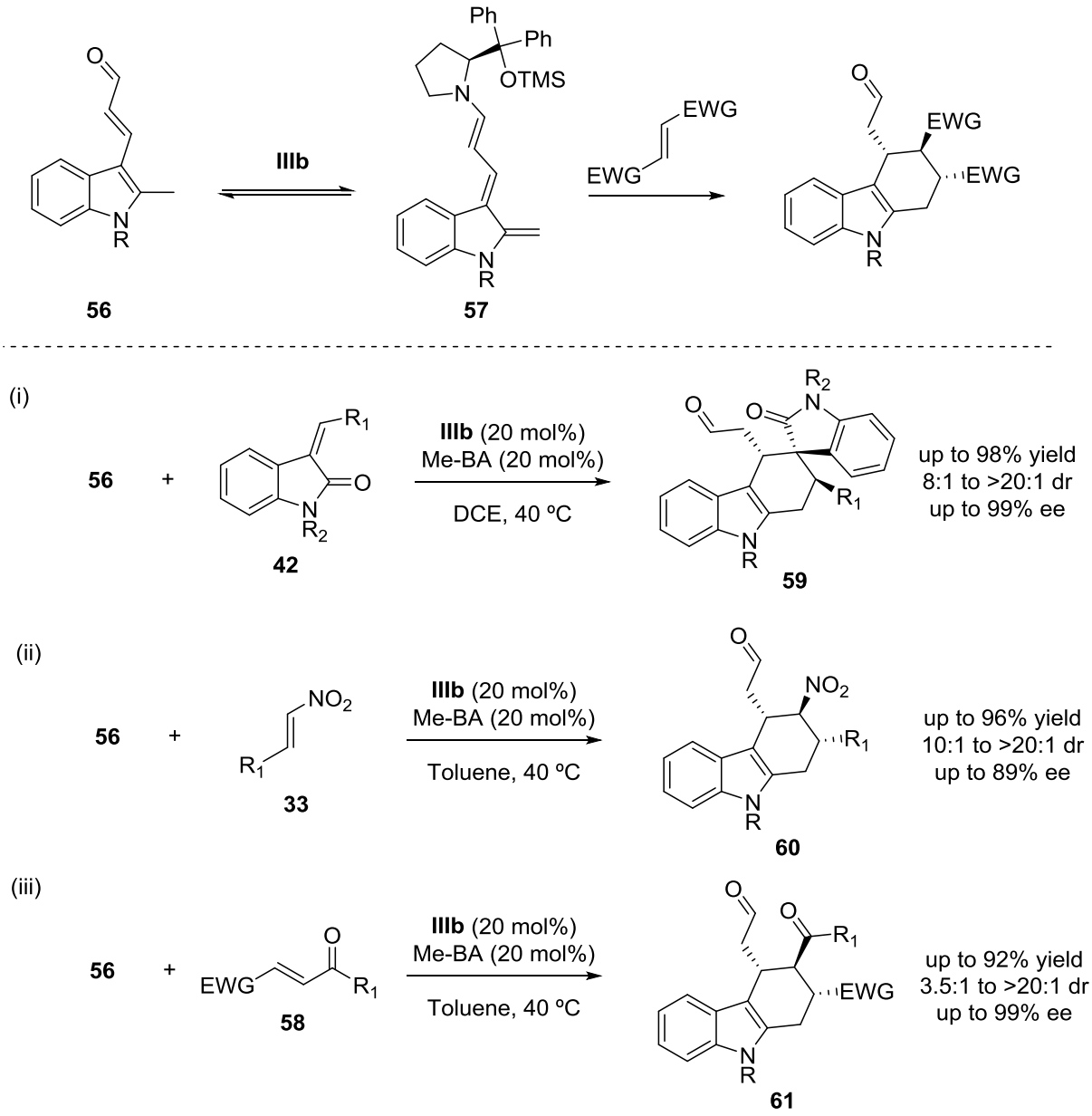


Scheme 1.23 - Asymmetric Diels-Alder reactions via cross- trienamine intermediates between cyclic dienal **50** and (i) olefinic oxindoles **42**, (ii) olefinic azlactones **44** and (iii) vinyl bis-sulfones **52**.

Recently, Melchiorre's group studied the trienanmine concept for Diels-Alder reactions to produce tetrahydrocarbazole derivatives using non-traditional disconnections[32].

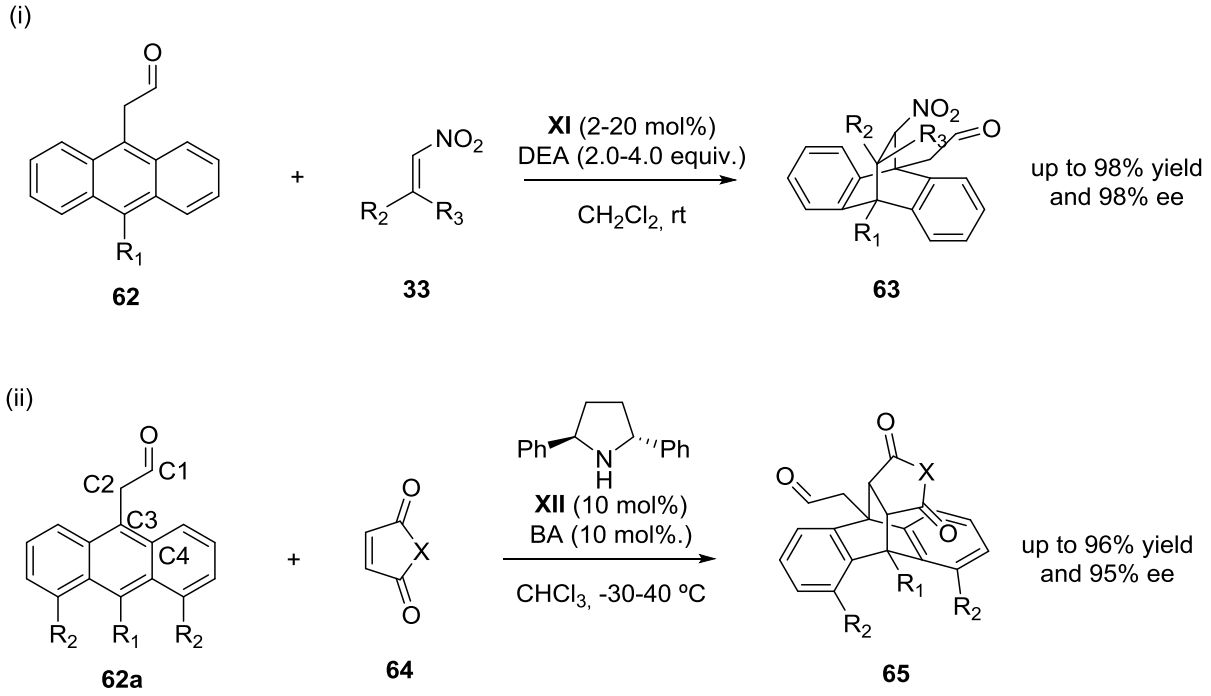
For this approach Melchiorre *et al.* used enal **56** which upon condensation with catalyst **IIIb** gave the trienamine intermediate **57**. This trienamine was then subjected to a series of dienophiles such as olefinic oxindoles **42**[32], nitroolefins **33**[32], and keto-containing dienophiles **58**[33] to produce the respective tetrahydrocarbazoles with good to excellent diastereoselectivities and excellent enanteoselectivities (Scheme 1.24).

Remarkably the condensation between the heteroaromatic system with an aminocatalyst results in a dearomatization of the heteroaryl system at mild conditions. Upon reaction with an appropriate dienophile the system is re-aromatized yielding highly complex products. The same group showed later that compounds similar to **61** can undergo *in situ* cyclization if a NHC catalyst is present affording a library of *trans*-fused tetracyclic products in near enantiopurity[33].



Scheme 1.24 - The synthetic potential of the trienamine-based indole-2,3-quinodimethane **56** strategy with: (i) olefinic oxindoles **42**; (ii) nitroolefins **33**; and (iii) keto-containing dienophiles **58**.

More recently, Jørgensen's group employed the same dearomatization principle with trienamine intermediates by the use of an anthracene derivative[34]. Anthracenes and derivatives are known to undergo Diels-Alder reactions with suitable dienophiles. However, high temperatures are often required to overcome the large energetic barrier to achieve the desired dearomatization[35]. It was then rationalized by the authors that the introduction of an acetaldehyde moiety in the position 9 of anthracene **62** could allow the room temperature Diels-Alder reaction to occur catalyzed by an appropriate aminocatalyst. Therefore, highly enanteoselective Diels-Alder reactions were developed using either a steric shielding catalyst ((2*R*,5*R*)-2,5-diphenylpyrrolidine) **XII** or the bifunctional H-bond directing aminocatalyst **XI** (Scheme 1.25).



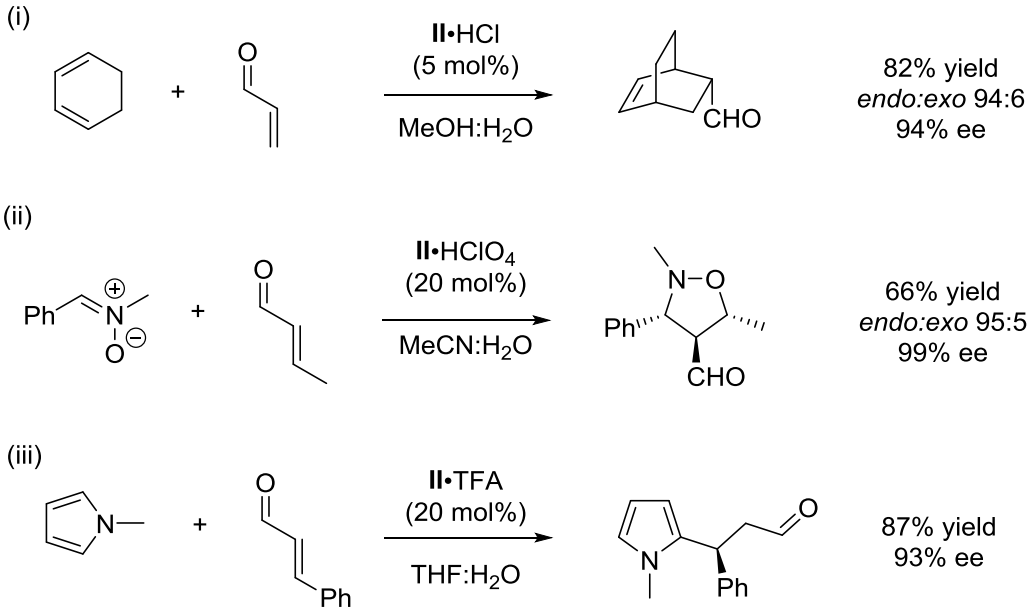
Scheme 1.25 - Anthracene derivative Diels-Alder reaction (i) H-bond-assisted, and (ii) steric induced differenciation.

When dienophiles with good H-bond acceptors are employed the squaramide-based catalyst **XI** showed to provide the best results[34]. The squaramide moiety of the catalyst recognizes and activates **33** by LUMO-lowering, while the formation of a catalyst-bound enamine in conjugation with the anthracene ring raises the HOMO energy of the polyaromatic ring. It was also revealed in this work that the aromaticity in the anthracenyl ring decreases upon condensation with the catalyst due to a distortion in the planarity of the polycyclic structure when the enamine is formed.
In contrast, when poor H-bond acceptors are used the catalyst **XII** is shown to exhibit the best reactivity[36]. Intriguingly, the observed stereo-induction does not arise from direct steric shielding provided by the catalyst. Instead, it was shown by the authors by DFT-studies, that different dienophile approaches may trigger different conformations of the catalyst-bound intermediate. A discrepancy in the C1-C2-C3-C4 dihedral in these conformations results in different degrees of activation of the anthracene ring hence favoring the formation of the one enantiomer of **65**.

I.3 - LUMO-lowering strategies

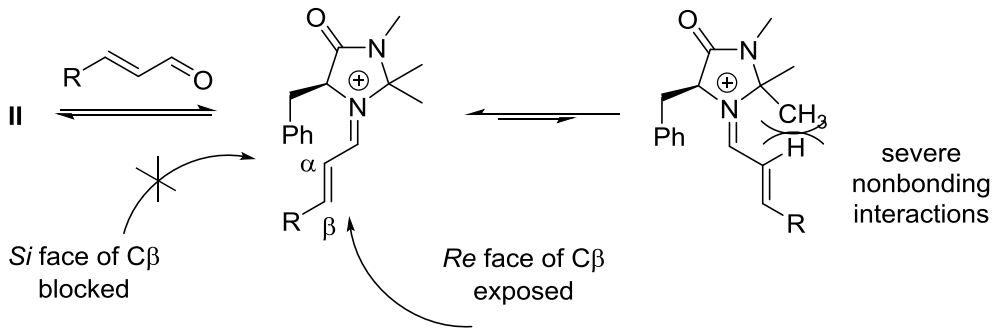
I.3.1 - Iminium-ion and vinylogous iminium-ion mediated catalysis

As mentioned previously, the first organocatalytic process involving an iminium-ion intermediate was described by MacMillan *et al.*[3]. MacMillan's first repost on a Diels-Alder reaction involving α,β-unsaturated aldehydes catalyzed by an imidazolidinone (**II**) marked a milestone in organocatalysis.
This activation mode in aminocatalysis exploits the reversible condensation between a chiral amine and an α,β-unsaturated aldehyde to form an electron poor intermediate - iminium-ion - which has a lower LUMO energy of the π-system than the starting aldehyde making this species susceptible to a nucleophilic attack[6].
Further studies from MacMillan's group established the effectiveness of the imidazolidinone derivatives to promote several transformations of α,β-unsaturated aldehydes in a highly enanteoselective fashion (Scheme 1.26)[11, 37]. It should also be noted that the nature of the anion of the catalytically active salt is essential for modulating both reactivity as well as stereoselectivity.



Scheme 1.26 - Asymmetric iminium catalysis by imidazolidinone **II**: (i) Diels-Alder reaction[3]; (ii) [3+2]-cycloaddition with nitrones[37]; and (iii) Friedel-Crafts alkylation of pyrroles[38].

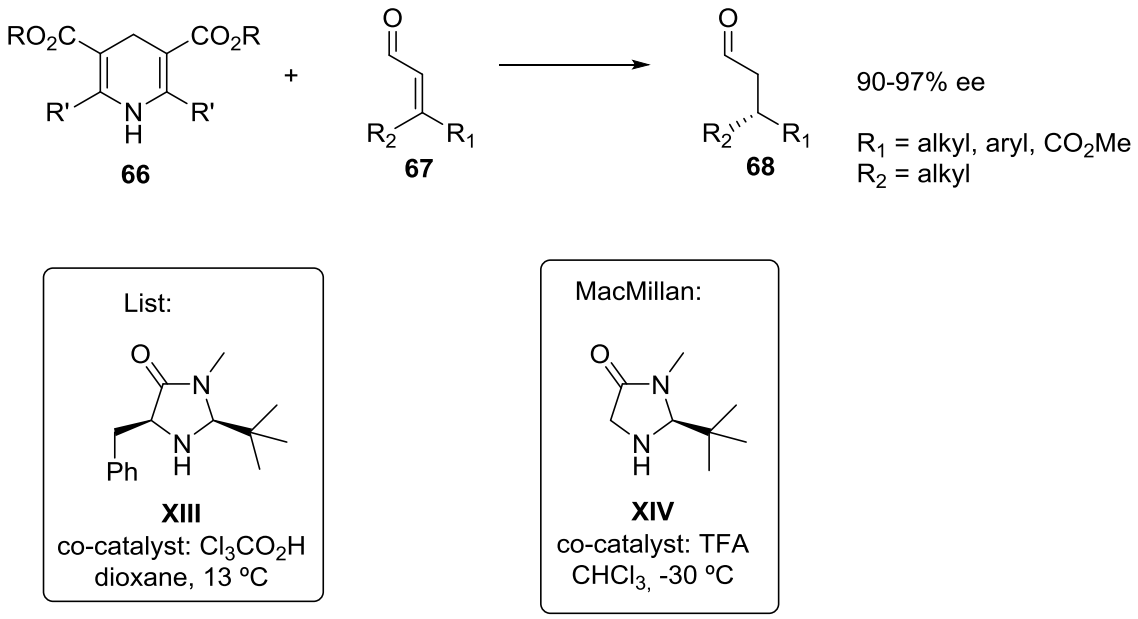
MacMillan's imidazolidinoe catalyst is capable of high levels of both configurational control and π-facial discremination (Scheme 1.27). The activated iminium intermediate predominantly exists in the *E* conformation to avoid problematic interactions with the *gem*-dimethyl groups on the catalyst. The selective π-facial blocking framework of the catalyst is a benzyl group which leaves the *Re* face of the Cβ of the iminium-ion exposed for the nucleophilic attack, therefore resulting in high enanteoselectivities.



Scheme 1.27 - Control of the configuration and π-facial differentiation provided by the imidazolidinone in an iminium-ion.

One of the most impressive and important developments in iminium-ion mediated catalysis has been offered by the metal-free, organocatalytic asymmetric transfer hydrogenation of α,β-unsaturated aldehydes. The metal-catalyzed hydrogenations of double bonds are by far the most predominant asymmetric transformations applied to industrial processes. Their usefulness was recognized by the award of the Nobel Prize in Chemistry to Knowles and Noyori in 2001.

The development of organocatalytic asymmetric reductions with hydride would thus be useful to solve toxicity concerns about the complete removal of metal impurities. The research groups of MacMillan and List demonstrated that iminium catalysis is a suitable strategy for accomplishing the highly enanteoselective reduction of enals by using synthetic Hantzsch dihydropyridines **66** as hydride donors (Scheme 1.28)[39].



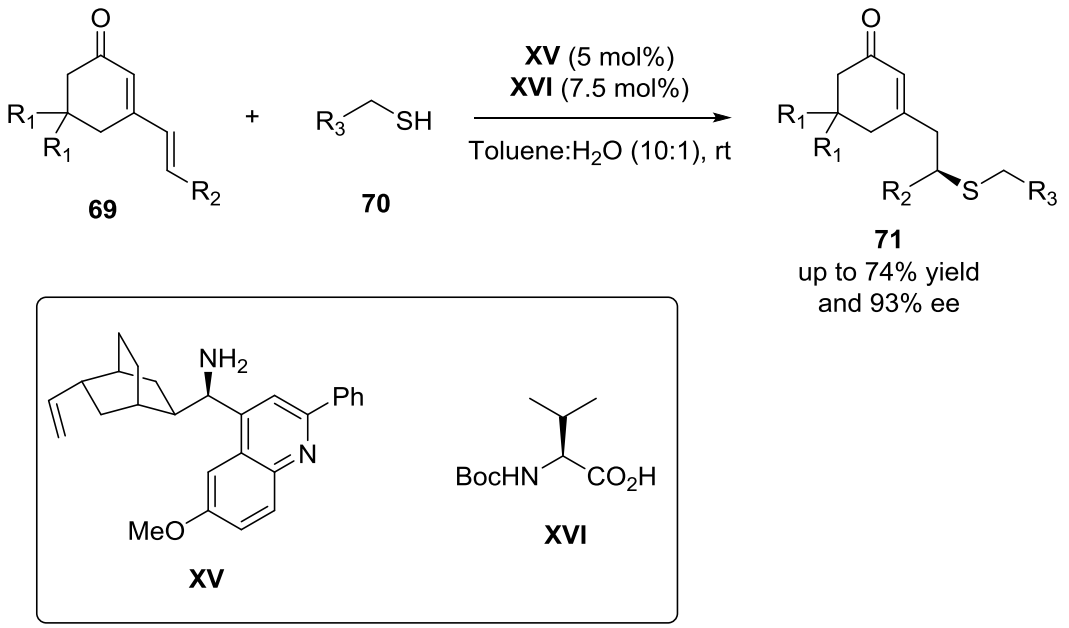
Scheme 1.28 - Iminium-ion catalyzed transfer hydrogenation.

The propagation of the HOMO-raising electronic effect through the π-conjugated systems in poly-unsaturated carbonyl compounds has been proven, in the previous section, as a well establish concept. However, the application of the same vinylogy principle to the iminium-ion mediated catalysis has only recently been explored. The successful transmission of the LUMO-lowering effect within the extended π-system of 2,4-unsaturated carbonyls would not only be interesting from a conceptual point of view but could also address a synthetically difficult issue for which few catalytic methods are available: the direct and stereoselective functionalization of unmodified carbonyl compounds at the remote δ-position[40].

The difficulties in realizing such 1,6-additions lie in identifying a chiral amine catalyst that could ensure configurational control and π-facial discrimination of the extended iminium-ion intermediate[41].

Melchiorre's group, inspired by some of their work on dienamine activation of cyclic enones[42] decided to apply the same cinchona alkaloid derivative (**VII**) catalyst to establish the feasibility of the vinylogous LUMO-lowering activation startegy.

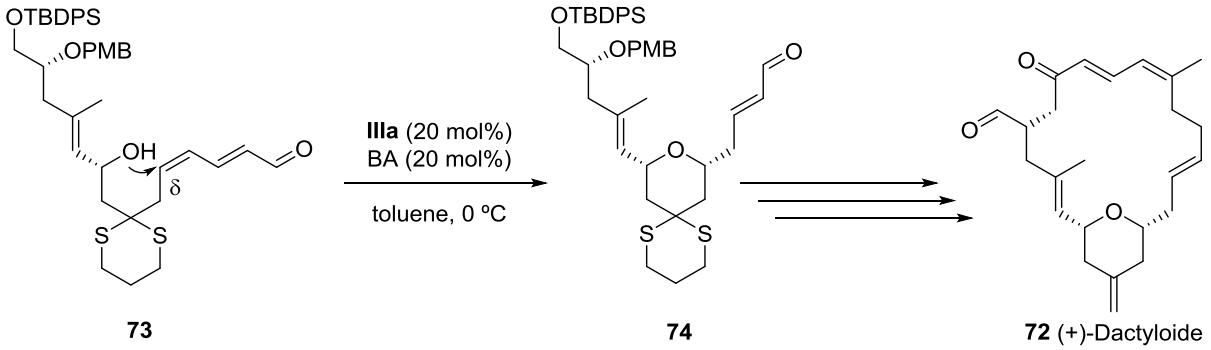
The successful realization of the vinylogy iminium-ion strategy enable the highly δ-selective addition of sulfur nucleophiles **70** to cyclic enones **69** affording mercaptoenones **71**. The use of a combination of a modified cinchona alkaloid **XV**[43] and boc-protected valine **XVI** allowed the reaction to proceed with high enanteoselectivities (Scheme 1.29)[44].



Scheme 1.29 - Enanteoselective 1,6-addition of thiols **70** to cyclic dienones **69** through vinylogous iminium-ion activation**.**

In the 1,6-addition of thiols to the cyclic dienones, the inherent steric bias of the β-substituent in **69** provided a control element for securing the δ-site selectivity by supressing the competing 1,4-addition. Steric bias is, however, not the only strategy available for guiding the regioselectivity of aminocatalyzed 1,6-addition.

The thermodynamic stability of the product obtained is also an important factor. This was showcased in the total synthesis of (+)-dactyloide **72** (Scheme 1.30). Indeed, the group of Kim and Hong demonstrated that the advanced intermediate **73** selectively underwent an intramolecular 1,6-addition to form a six-membered ring in **74**, whereas the potential concurrent 1,4-addition would lead to the thermodynamically less favored eight-member ring and therefore is not observed[44].



Scheme 1.30 - A diastereoselective intramolecular 1,6-addition of an alcohol to a conjugated dienal catalyzed by aminocatalyst **IIIb** en route to the enanteoselective total synthesis of (+)-dactyloide **72.**

With all these advances in aminocatalysis, some questions still remain to be answered, such as where do these remote activation strategies end? In the next section a new activation mode will be presented and demonstrated as an important activation concept in asymmetric organic synthesis.

Chapter II - Presentation and Discussion of the Results

II.1 - Tetraenamine-mediated [4+2]-cycloadditions

One of the challenges in modern organic chemistry is the development of new activation concepts. In the following section will be presented a new concept in aminocatalysis - tetraenamine activation. This new activation concept was used for the construction of highly functionalized spirocyclic oxindoles with four stereo centers. In addition, several intermediates could be observed and/or isolated giving insights into a stepwise mechanism of the explored [4+2]-cycloaddition reaction. As opposed to dienamine catalysis, where a 1,4-reactivity usually traps the catalyst (Scheme 1.11 in the Introduction), a clean and fast reaction is observed with the tetraenamine system which represents a new reactivity and selectivity concept in aminocatalysis.

In order to obtain the desired tetraenamine intermediate 2-(cyclohepta-1,3,5-trien-1-yl)acetaldehyde (**75**) was synthesized and upon condensation with the TMS-protected diarylprolinol ether catalyst **IIIa** yield the desired tetraenamine intermediate The aldehyde moiety being out of conjugation with the triene system, resulted in a fast condensation with **IIIa** affording a fully conjugated system. Initial studies by NMR spectroscopy were performed to confirm the presence of the proposed tetraenamine. Mixing aldehyde **75** with the aminocatalyst **IIIa** in a 1:1 ratio (0.2 M in $CDCl_3$) in the presence of 20 mol% *o*-FBA and 4Å MS gave the tetraenamine **76** in the s-*trans* conformation (confirmed by the NOESY spectrum, see annexes) in a clean and almost complete reaction (Figure 2.1).

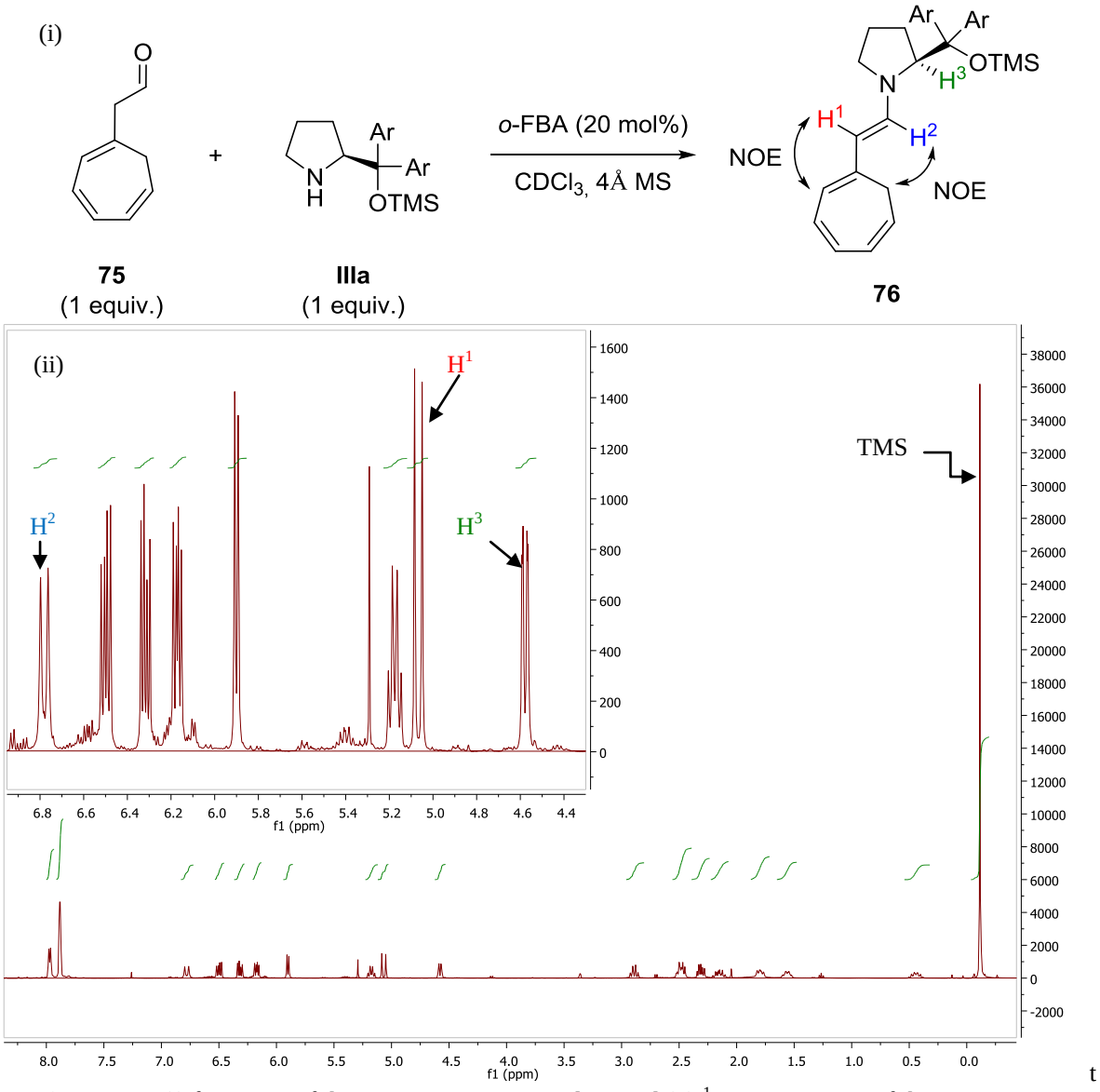
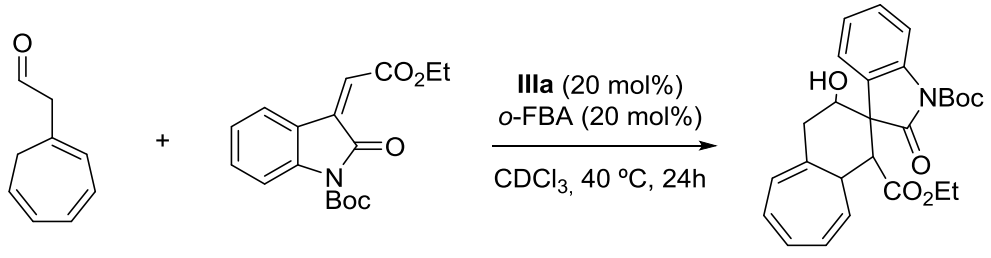


Figure 2.1 - (i) formation of the tetraenamine intermediate and (ii) ^{1}H NMR spectra of the tetraenamine intermediate with the unsaturated region expanded.

Upon observing the formation of the tetraenamine intermediate **76** it was decided to study its reactivity towards the [4+2]-cycloaddition reaction with 3-olefinic oxindoles **42** (Scheme 2.1).



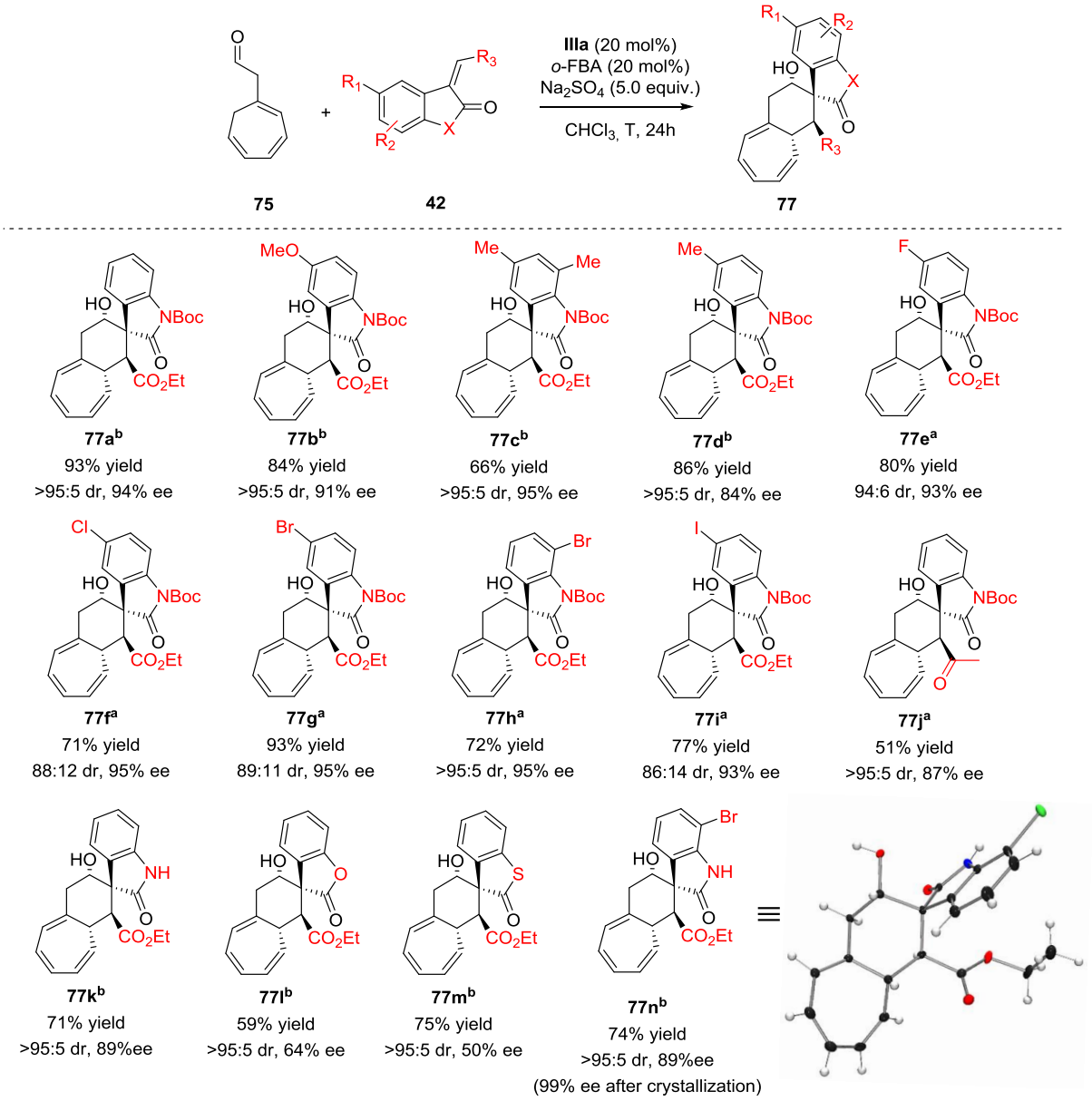
75 **42a** **77a**
93% yield
>95:5 dr
94% ee

Scheme 2.1 - Tetraenamine mediated [4+2]-cycloaddition between aldehyde **75** and the 3-olefinic oxindole **42a** affording the cycloadduct **77a**.

Under optimized conditions (data not included) oxindole **42a** reacted smoothly affording the corresponding cycloadduct **77a** in 93% yield, >95:5 dr and 94% ee. Cycloadduct **77a** contains a highly functionalized six-member ring with an annulated seven-member ring representing a new class of spirocyclic cyclohexanes structures. These structures which contain an all-carbon quaternary stereocenter are the core of several natural products and biological active compounds. Moreover the oxindole moiety is a well known feature in many natural products with biological activity[45].
To test the generality of the tetraenamine mediated [4+2]-cycloaddition several oxindoles were used as starting materials (Scheme 2.2).
Delightfully the reaction turned out to be very general as different structural variations on the 3-olefinic oxindoles **42** gave rise to the desired cycloadduct **77** with high enanteoselectivities (84-95% ee), moderate to good yields (51-93%) and excellent diastereoselectivities on all examples (86:14 to >95:5 dr). The variations introduced in the oxindoles starting materials included electron-rich (**42b-d**) and -poor (**42e-i**), mono- or disubstituted aromatics rings as well as unprotected amines (**42k,n**), benzofuranone (**42l**) and benzothiophenone (**42m**) (Table 2.1). Depending on the substituents the reaction temperature could be lowered to rt. The absolute configuration of the cycloadduct **77n** was determined by X-ray analysis (Scheme 2.2, for more information see Experimental Procedure) while the remaining products were assigned by analogy.

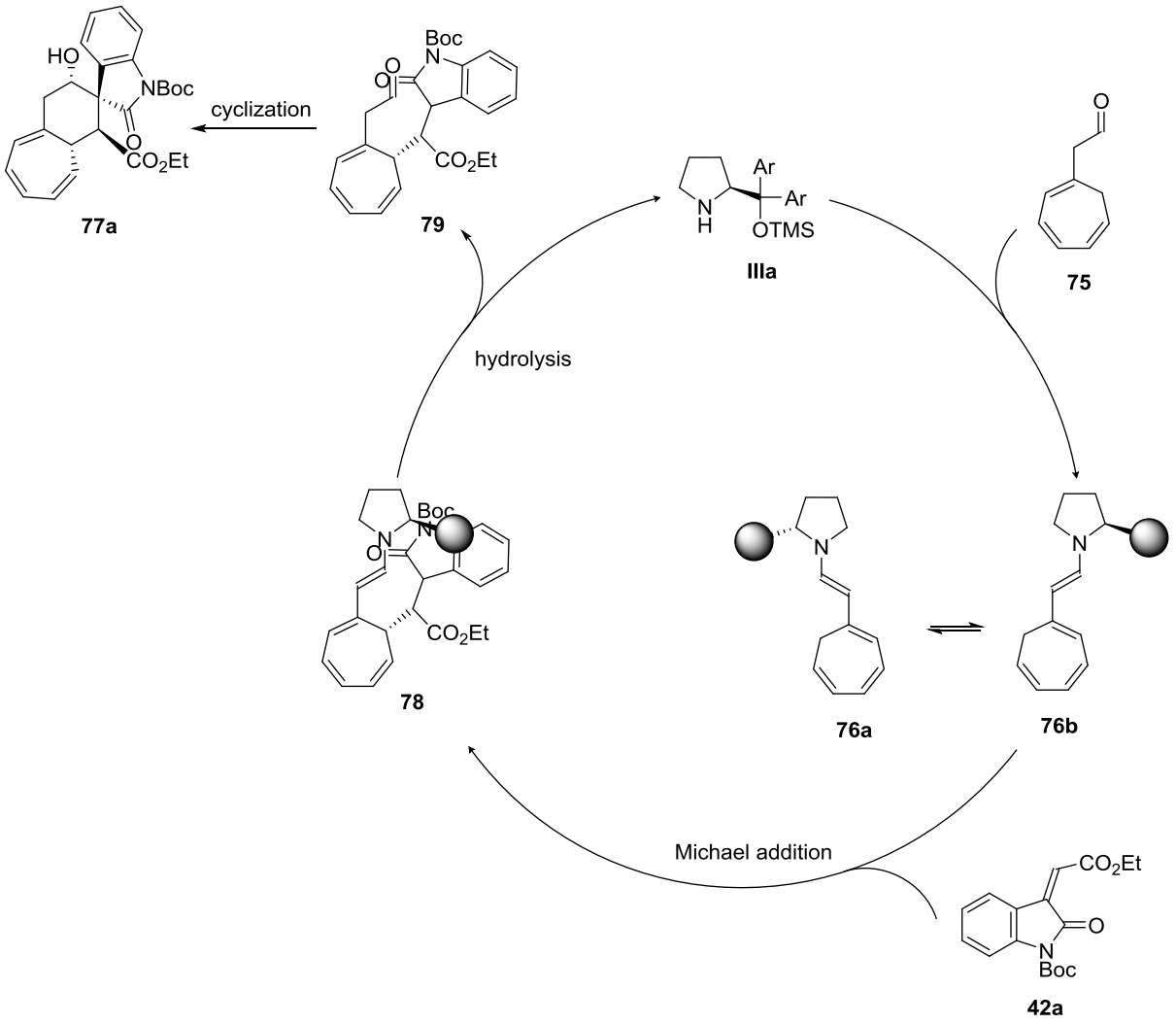
Table 2.1 - Structure of the starting oxindoles **42a-n**.

Oxindole	R_1	R_2	R_3	X
42a	H	H	CO_2Et	NBoc
42b	5-OMe	H	CO_2Et	NBoc
42c	5-Me	7-Me	CO_2Et	NBoc
42d	5-Me	H	CO_2Et	NBoc
42e	5-F	H	CO_2Et	NBoc
42f	5-Cl	H	CO_2Et	NBoc
42g	5-Br	H	CO_2Et	NBoc
42h	H	7-Br	CO_2Et	NBoc
42i	5-I	H	CO_2Et	NBoc
42j	H	H	COMe	NBoc
42k	H	H	CO_2Et	NH
42l	H	H	CO_2Et	O
42m	H	H	CO_2Et	S
42n	H	7-Br	CO_2Et	NH



Scheme 2.2 - Scope of the tetraenamine-mediated [4+2]-cycloaddition. All reactions performed in a 0.1 mmol scale. a) reaction performed at rt; b) reaction performed at 40 °C. Yields after isolation by FC are given. dr determined by ^{1}H NMR spectroscopy. ee determined by UPC^{2}.

Some preliminary experiments were performed to assess the mechanism of the tetraenamine-mediated [4+2]-cycloaddition. Mixing aldehyde **75** and catalyst **IIIb** in a 1:1 ratio, in the presence of 4Å MS, followed by the addition of 1.0 equiv. of oxindole **42a** allowed the isolation of intermediate **78** (Scheme 2.3, when catalyst **IIIa** was used the intermediate decomposed in the column). This experiment in conjugation with the work independently done by Houk *et al.*[46] suggested a stepwise mechanism in which the tetraenamine would add to the oxindole in a Michael addition fashion followed by hydrolysis of the catalyst to give intermediate **79** which would then cyclize to afford product **77a** (Scheme 2.3).



Scheme 2.3 - Preliminary proposed mechanism for the tetraenamine-mediated [4+2]-cycloaddition.

In order to account for the stereochemistry observed in the final product, it was also rationalized in this mechanism that tetraenamine **76** would have to undergo a rotation around the exo-cyclic C - C bond to produce the s-*cis* conformer **76b**, even though, in the ^{1}H NMR experiment previously described, the more stable s-*trans* conformer **76a** was the only one observed.

Further work seemed to support this mechanism. A kinetic study was performed by NMR spectroscopy, using oxindole **42e** (Figure 2.2). Oxindole **42e** was chosen as it made possible to follow the reaction in both ^{1}H- and ^{19}F-channels, with this last one providing a less complex and easier spectrum to analyze.

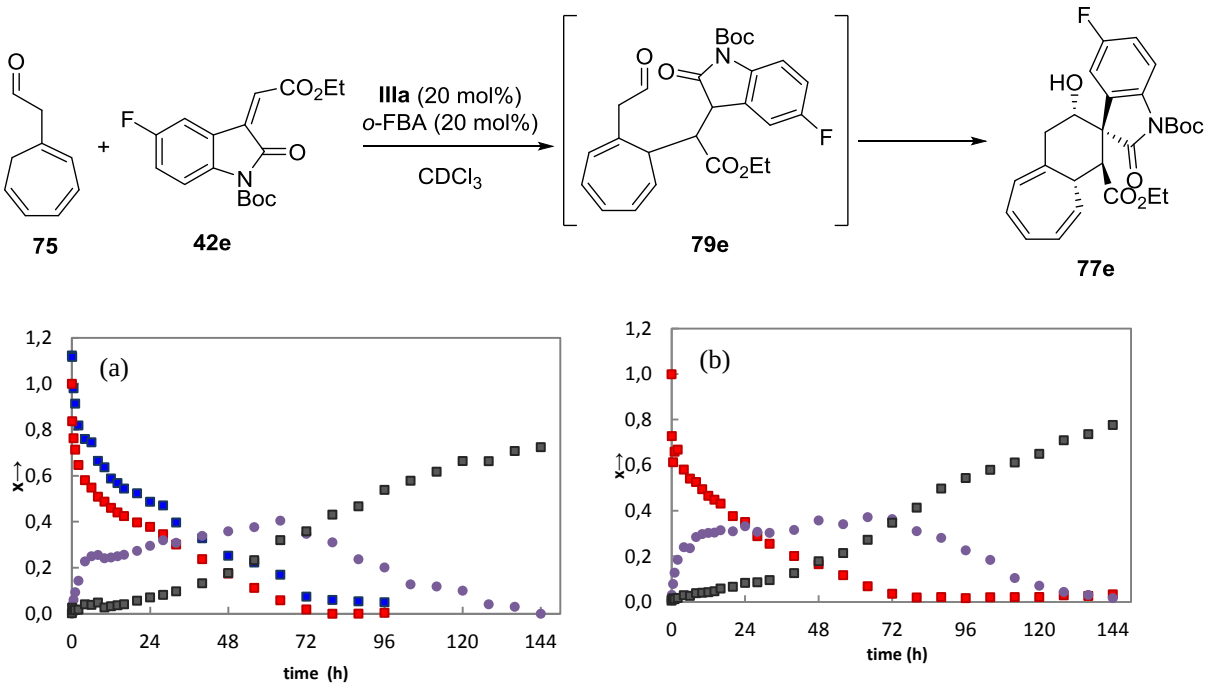


Figure 2.2 - Kinetic studies followed by (a) ^{1}H NMR and (b) ^{19}F NMR spectroscopy. (blue = aldehyde **75**, red = oxindole **42e**, purple = intermediate **79e** and black = cycloadduct **77e**; 1,3,5-tris(trifluoromethyl)benzene was used as internal standard).

In this experiment was observed the fast consumption of both starting materials while an intermediate specie was being rapidly formed. This intermediate was assumed to be compound **79** which would slowly be consumed as the product was being formed. The rate determining step for this reaction was then thought to be the cyclization step.

However, computational studies proved this preliminary mechanism to be not entirely accurate. In the new proposed mechanism, the overall reaction proceeds in a similar way as previously described but different intermediates have to be considered.

The new computational data fit the NMR experiments previously described as well as the proposed conformational equilibrium between the tetraenamine conformers **76a** and **76b** which account for the stereochemistry of the final product. These studies also give insights into the reason why this reaction turns out to be highly diastereoselective.

Computational studies (data not included) on the conformational preference of a simplified model of **76** (Figure 2.3) show **A**, the s-*trans* conformer to be the lowest energy conformer, while **B**, the s-*cis* conformer, is only 0.9 kcal mol^{-1} higher in energy. Addition of oxindole **C** to the γ-carbon of **A** was shown to have a barrier of 21.1 kcal mol^{-1} and forms a zwitterionic intermediate **D** that is 15.8 kcal mol^{-1} higher in energy than the reactants. Addition of **C** to the γ-carbon of **B** has a barrier of 17.8 kcal mol^{-1}. The fact that the activation energy of the addition to the γ - carbon of **A** is 3.3 kcal mol^{-1} higher than the addition to **B** suggests that the formation of **D** is unlikely to happen to any significant extent. The calculations also show that the cyclization of **B** and **C** takes place in a stepwise manner.

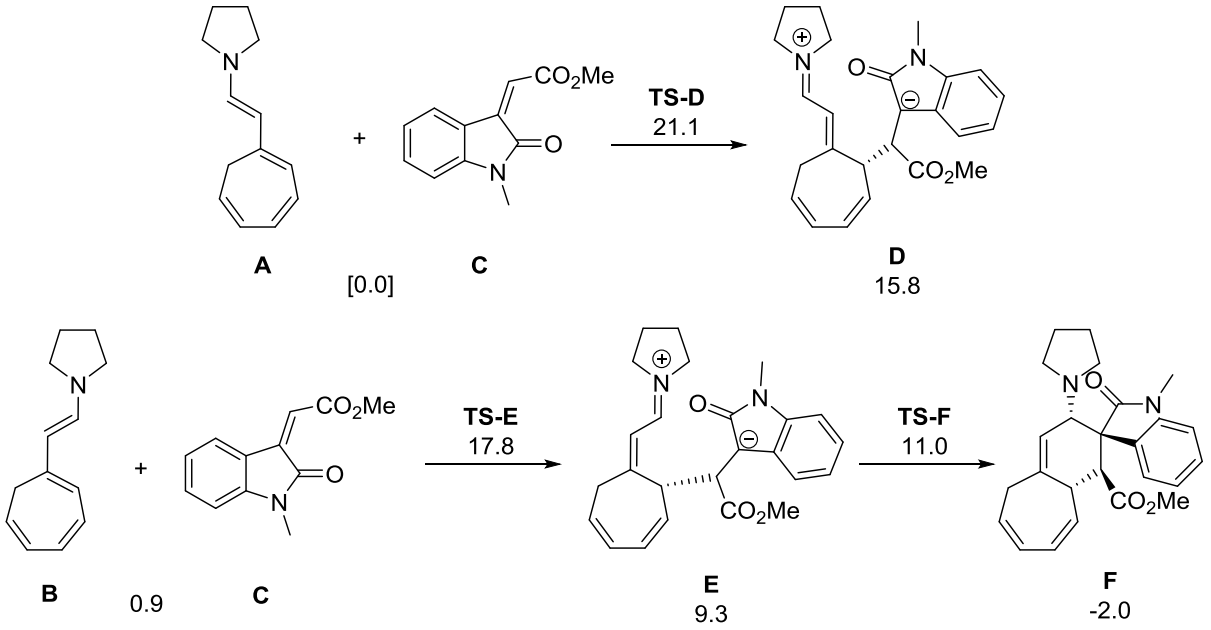
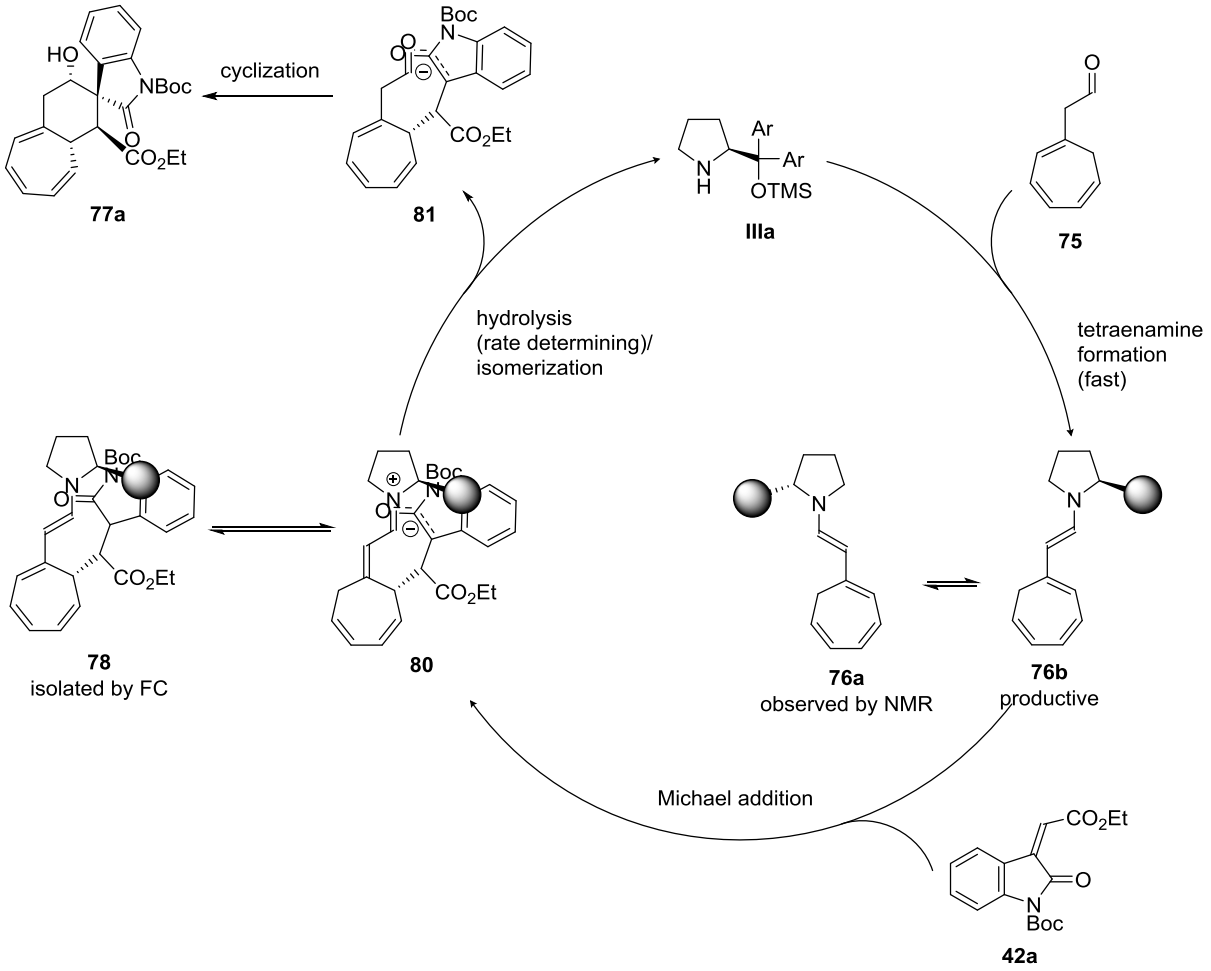


Figure 2.3 - Calculated reaction path for the reactions of two isomers of the tetraenamine intermediate with an oxindole. Activation energies are Gibbs free energies (kcal mol^{-1}) from IEFPCM-wB97xD/6-31+G(d,p) in $CHCl_3$.

As mentioned before, when 1.0 equiv. of oxindole **42a** and 4Å MS were added to the formed tretraenamine, full conversion of the oxindole is observed after 3 h at rt. Quenching the reaction after this step by column chromatography enable the isolation of **78** (Scheme 2.3). In contrast to that, the removal of the molecular sieves and the addition of H_2O (2.0 equiv.) and of an aldehyde (2.0 equiv.) affords product **77a** after 14h at 40 °C. The reaction rate was found to increase with the amount of catalyst, aldehyde and H_2O, suggesting all of them to be involved in the rate determining step. Based on these observations the hydrolysis is assumed to be that step.

The isolation of intermediate **78** supports that this reaction occurs in a stepwise manner via the zwitterionic species **80** in contrast to what was previously suggested. This is consistent with computational data which shows the addition and cyclization occur in two steps (Figure 2.3). Cyclization of the zwitterionic intermediate **E** occurs readily with a barrier of 11.0 kcal mol^{-1}. This cyclized product **F** traps the catalyst and does not lead to the observed product. However, this cyclization step is readily reversible with a barrier of 13.0 kcal mol^{-1}.

With this new results a new mechanism was proposed for the [4+2]-cycloaddition which proceeds via tetraenamine formation, Michael addition, catalyst hydrolysis/isomerization and cyclization sequence (Scheme 2.4).



Scheme 2.4 - Proposed mechanism via a zwitterionic species **80.**

The high diastereoselectivity of this cyclization reaction is impressive given that both experimental and computational results suggest the cyclization step occurs after hydrolysis of the catalyst and that all three double bonds in the product **77a** are contained within the seven-membered ring. To understand how the high diastereoselectivity is achieved it was examined a series of model systems computationally (Figure 2.4). The first system **G** contains an unsaturated aldehyde, in which conjugation of the exocyclic handle would prevent rotation and therefore provide only one diastereomer of the cyclized product.

However, **G** is not the favored isomer. Calculations reveal that model **H**, which has the three endocyclic double bonds in conjugation is favored over **G** by 1.7 kcal mol^{-1}. Cyclization of **H** is also kinetically favored over cyclization of **G** by 8.2 kcal mol^{-1}. As **H** has free rotation about the exocyclic C - C bond it was also considered the reaction of its isomer **J**. Unlike the cyclization of **H**, **J** would yield a different diastereomer of the product. Cyclization of **J** occurs with a barrier of 12.4 kcal mol^{-1}. This barrier is 3.2 kcal mol^{-1} higher than the one of **H**. The difference in the energies between these two cyclizations results from steric clashes between the oxindole and the seven membered ring in **J** and explains the high selectivity of the second addition step (Figure 2.4).

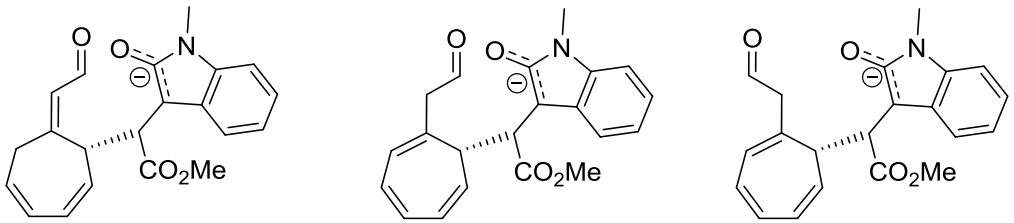
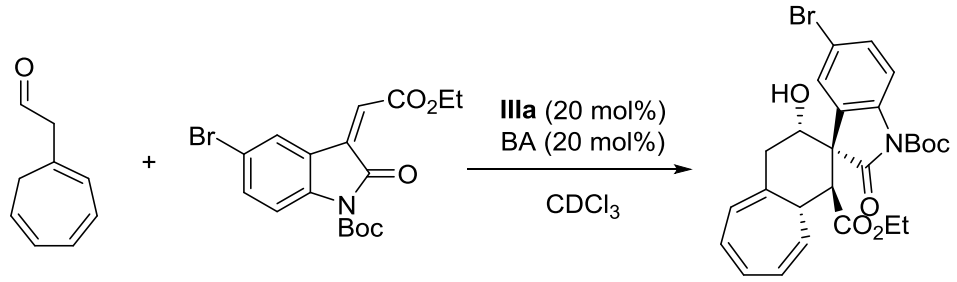


Figure 2.4 - Energies of uncyclized intermediate **81** (**G**) and its isomers (**H** and **J**, simplified models). Energies are Gibbs free energies (kcal mol-1) from IEFPCM-wB97xD/6-31+G(d,p).

Intriguingly, previous work had showed that the dr decreased with the presence of water (Table 2.2) and the addition of 5.0 equiv. of Na_2SO_4 was crutial to obtain high dr's in all examples (Scheme 2.2). Even though, no other salts were tested one can speculate that the sodium ion plays an important role in the diastereoselectivity of this reaction forming some kind of coordination between the oxygen of the aldehyde and the enolate of the oxindole trapping intermediate **H** in a specific conformation. Still, this results support that the presence of some water is necessary in the reaction as the addition of 4Å MS leads to no reaction.

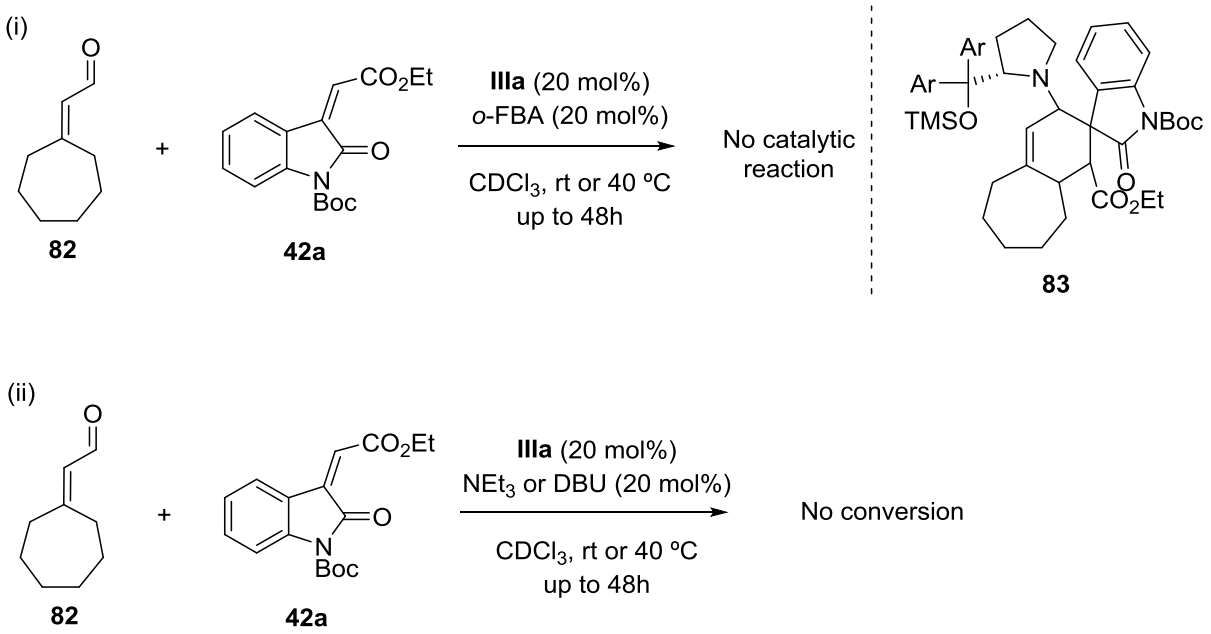
Table 2.2 - Effect of water on the tetraenamine mediated [4+2]-cycloaddion between oxindole **42g** and aldehyde **75**.



Conditions	4Å MS[a]	Dry vial, dry $CDCl_3$, 5.0 equiv. of Na_2SO_4	Dry vial, dry $CDCl_3$	Standard conditions	Addition of 5.0 equiv. of H_2O	Addition of 10 equiv. of H_2O
dr	—	89:11	86:14	83:17	75:25	66:33

(a) no reaction.

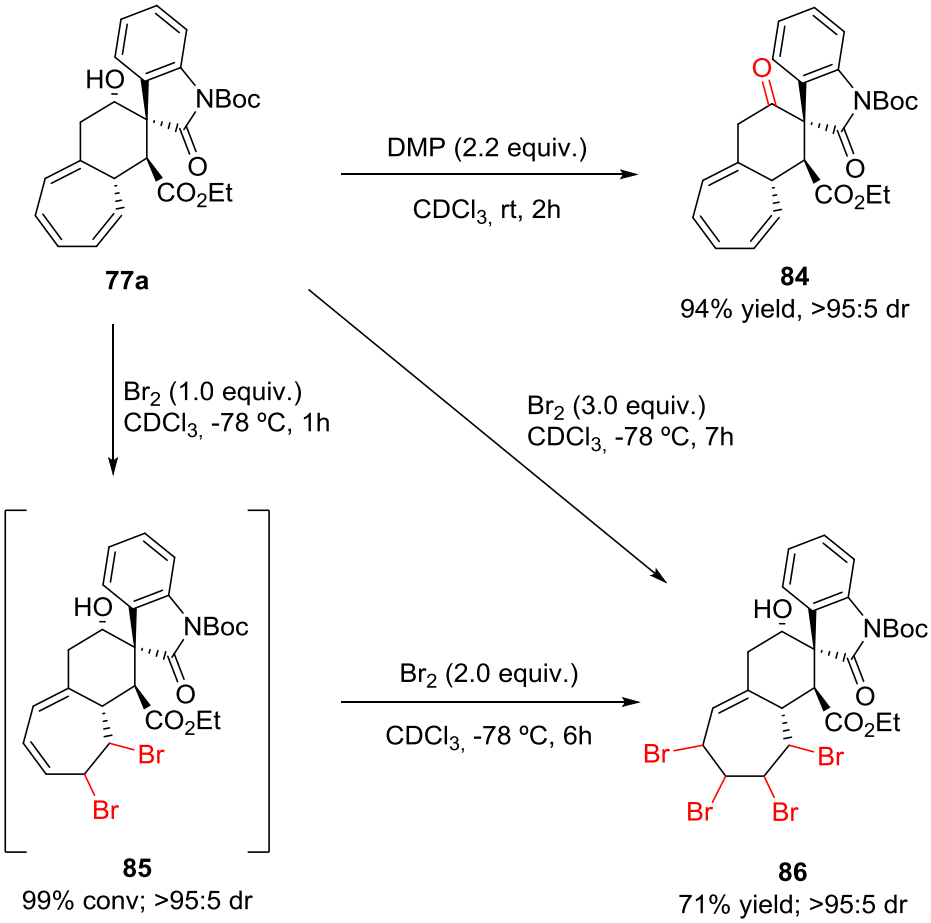
To demosntrate the novelty of the tetraenamine-mediated reactivity, it was compared with the corresponding dienamine activated process using enal **82**. Under similar reaction conditions no catalytic reaction takes place. The only consumption of starting materials is based on the formation of the 1,4-addition product **83** in which the catalyst is trapped (Scheme 2.5, eq. i). Furthermore, a basic additive was used instead of an acid (NEt_3 and DBU were tested) in an attempt to see if it was possible to eliminate the catalyst. However, no conversion was observed after 48 h at 40 °C (Scheme 2.5, eq. ii).



Scheme 2.5 - Comparison with the dienamine-activated process. (i) with an acid as additive. (ii) with a basic additive. Reaction performed on a 0.1 mmol scale either at rt or 40 °C over 48h. 1,4-addition product **83** was isolated under the same conditions using 1.0 equiv. of catalyst **IIIa.**

Having successfully developed and tested the tetraenmaine activation process the synthetic utilization of the obtained cycloadducts **77** was studied (Scheme 2.6).

Oxidation of **77a** under Dess-Martin conditions led to the highly substituted cyclohexanone **84** in excellent yield. Furthermore, it was possible to regioselectivily Brominate one of the C-C double bonds in the triene system using 1.0 equiv. of Br_2 at −78 °C (**85**)[47]. While compound **85** was stable in solution, the addition of an excess of Br_2 allowed us to modify a second double bound and isolate **86** in high yield. Delightfully the diastereoselectivity of both bromination protocols could be fully controlled leading to highly brominated compounds with six and eight stereocenters.

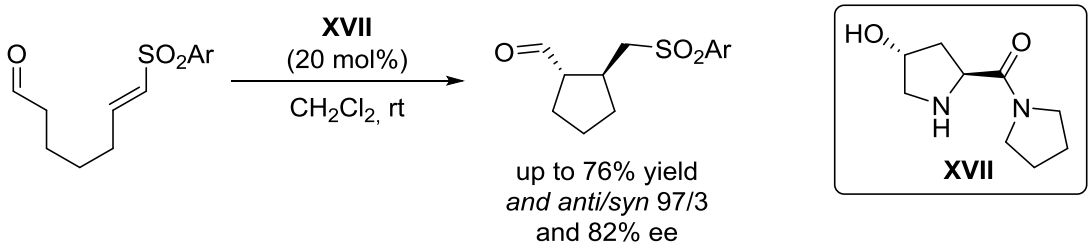


Scheme 2.6 - Transformations carried out on cycloadduct **77a.**

In summary a new activation concept has been introduced in organocatalysis - the tetraenamine. The reaction of 2-(cyclohepta-1,3,5-trien-1-yl)acetaldehyde with a TMS-protected prolinol catalyst generates a tetraenamine which was fully characterized in this work and the reaction of this intermediate with a 3-olefinic oxindole goes via a Michael addition-, hydrolysis of catalyst-, cyclization/isomerization sequence yielding highly functionalyzed spirocyclic oxindoles with 4 stereocenters in excellent enanteoselectivities (up to 95% ee) and diastereoselectivities (up to >95/5) and moderate to excellent yields (51-94%).
The synthetic applications of the obtained cycloadducts was also tested by a Dess Martin oxidation which afforded a highly functionalyzed cyclohexanone and by the regioselective bromination of the triene system of the seven-membered ring.

II.2 - Enamine-mediated asymmetric Michael addiction of aldehydes to vinyl sulfones

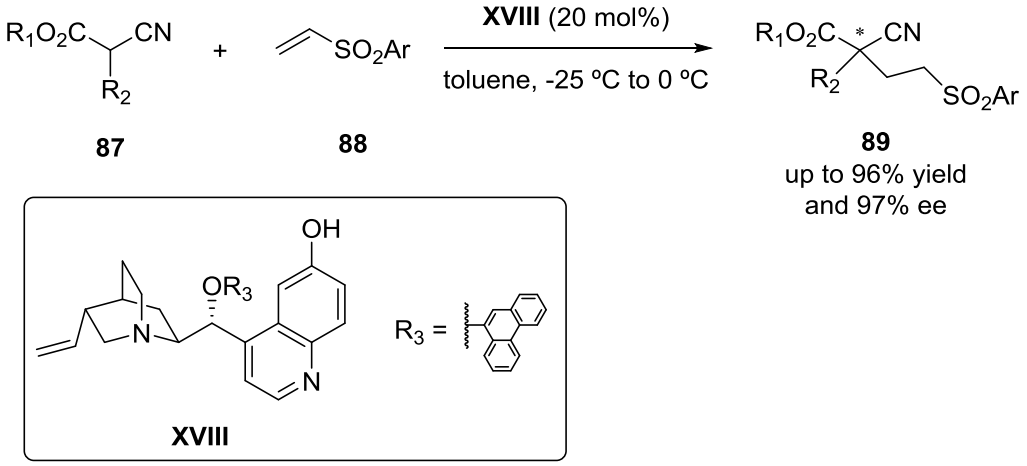
This project was aimed towards intermolecular Michael addition of aldehydes to vinyl sulfones by an enamine-mediated process catalyzed by chiral secondary amines.
Sulfones are versatile intermediates in organic synthesis allowing a great deal of transformations which can create interesting building blocks[48]. Thus, Conjugate additions of carbon nucleophiles to vinyl sulfones in parallel to nitroalkenes constitute a class of synthetically valuable C - C bond forming reactions. Although significant advancements have been made in the use of chiral auxiliaries, the realization of a highly enanteoselective catalytic conjugate addition of aldehydes to mono vinyl sulfones remains elusive[49].
In 2010 Alexakis *et al.*[50] described the organocatalytic intramolecular Michael addion of aldehydes to vinyl sulfunoes via an enamine-mediated process catalyzed by the aminocatalyst **XVII** (Scheme 2.7).



Scheme 2.7 - Intramolecular Michael addition reaction.

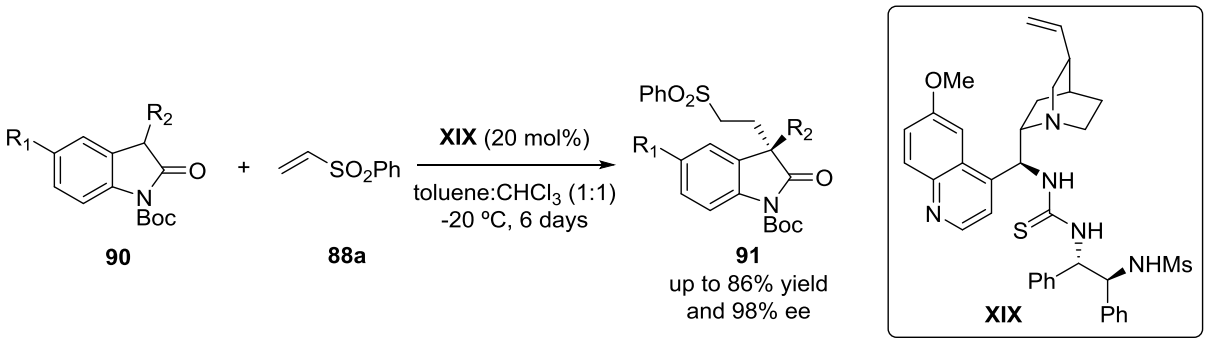
As shown in Scheme 2.7, the reaction does not prove to produce very good results as moderate yields and enanteoselectivities were obtained. The reaction was also slow (up to four days in most cases) and was restricted to electron deficient aromatic groups in the sulfone. The authors also concluded that the hydroxyl group present in the catalyst played an important role in this reaction as it was hypothesized that it would form H-bond with the sulfone. The use of a catalyst similar to **XVII** but without the hydroxyl moiety, afforded no product.

Li Deng *et al*[51] reported the intermolecular Michael addition of α-cianoacetates **87** to vinyl sulfones **88** catalyzed by a cinchona alkaloid derivative **XVIII** (Scheme 2.8).



Scheme 2.8 - Organocatalytic Michael addition of α-cyanoacetates **87** to vinyl sulfones **88** catalyzed by **XVIII**.

In 2011, the work from M. -X. Zhao and M. Shi[52] proved that 3-aryloxindoles **90** could be used as Michael donors to perform the addition to vinyl sulfones **88** catalyzed by a bifunctional thiourea-cinchona alkaloid catalyst **XIX** (Scheme 2.9).

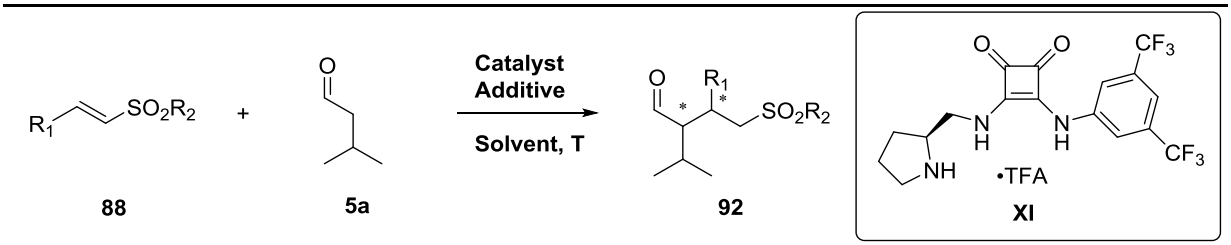


Scheme 2.9 - Organocatalytic Michael addition of 3-aryoxindoles **90** and phenyl vinyl sulfones **88a** catalyzed by **XIX.**

In both works presented by Deng and Zhao and Shi the authors take advantage of both basic and H-bond donor functionalities of the cinchona alkaloids derivatives to perform the described Michael addition.

Inspired by these works it was envisioned that the dual activation of a catalyst by HOMO-raising through enamine formation on the nucleophile and LUMO-lowering by H-bonding with the electrophile would enable the Michael addition of vinyl sulfones to aldehydes to take place.
With this in mind the squaramide catalyst **XI** developed by Jørgensen's group[25] was tested on the Michael reaction between isovaleraldehyde **5a** and a vinyl sulfone **88** (Table 2.3).

Table 2.3 - Reaction conditions for the organocatalyzed Michael addition of isovaleraldehyde (**5a**) to vinyl sulfones.



88 **5a** **92** **XI**

88a: R_1 = H; R_2 = Ph
88b: R_1 = H; R_2 = Me
88c: R_1 = Me; R_2 = CF_3

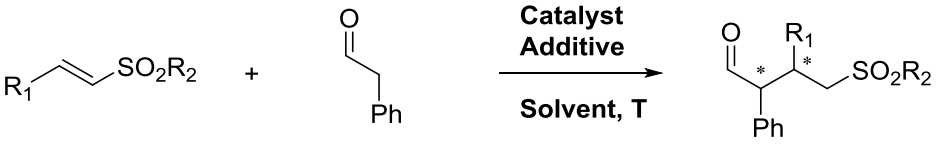
Entry	Substrate	Equiv. of Aldehyde	Catalyst	Additive	Solvent	T (°C)	Time (h)
1	**88b**	1.5 equiv.	**XI**	DMA/H_2O (1.0 equiv./2.8 equiv.)	CH_2Cl_2	rt	24
2[a]	**88a**	5.0 equiv.	**XI**	DMA/H_2O (1.0 equiv./2.8 equiv.)	CH_2Cl_2	reflux	120
3	**88a**	10 equiv.	**XI**	DMA/H_2O (1.0 equiv./2.8 equiv.)	CH_2Cl_2	rt	48
4	**88a**	10 equiv.	**XI**	—	$CHCl_3$/*i*-PrOH (9/1)	rt	96

All reactions carried out in 0.1 mmol scale in respect to the vinyl sulfone in the solvent (0.25 M). a) Reaction carried out with 0.3 equiv. of catalyst **XI**

In the first attempt was used 1.0 equiv. of methyl vinyl sulfone (**88b**) and 1.5 equiv. of isovaleraldehyde (**5a**) in the presence of 0.2 equiv. of catalyst **XI**, 1.0 equiv. of DMA and 2.8 equiv. of water. According to the literature[25] the presence of DMA is crucial to the catalyst activity due to the low solubility of the squaramide catalyst **XI** in ordinary organic solvents, as for the presence of water, it is described to increase the reaction rate by helping the hydrolysis of the catalyst. Unfortunately, under the reaction conditions described, no product was observed after 24 h and only starting materials were isolated (Table 2.3, entry 1).
It was then decided to change the substrate to phenyl vinyl sulfone (**88a**) and increase the loading of both the aldehyde (5.0 equiv.) and catalyst **XI** (0.3 equiv., Table 2.3, entry 2) and carried out the reaction under reflux. This approach also failed and the decomposition of the starting materials was observed.
Since the increment in temperature did not produce any result, the reaction temperature was lowered to rt and the loading of the aldehyde was increased to 10 equiv. Under these conditions decomposition of the catalyst was observed (Table 2.3, entry 3). Inspired by the work of Helma Wennemers *et al.*[53] the focus turned into a different solvent system and was then changed from CH_2cl_2 to a mixture of $CHCl_3$/*i*-PrOH (9/1; Table 2.3, entry 4). With this solvent system no DMA was added as one could observe that the catalyst was fully dissolved probably due to the presence of the *i*-PrOH.
However, under these reaction conditions, no desired reaction took place and instead the cross-aldol product was isolated in 12% yield (data not included). This low yield could be explained by the fact

that the starting aldehyde could still be observed by TLC analysis of the crude reaction mixture.
With the disappointing results obtained so far, it was decided to change the aldehyde from **5a** to phenylacetaldehyde (**5b**; Table 2.4).

Table 2.4 - Reaction conditions for the organocatalyzed Michael addition of phenilacetaldehyde (**5b**) to vinyl sulfones.



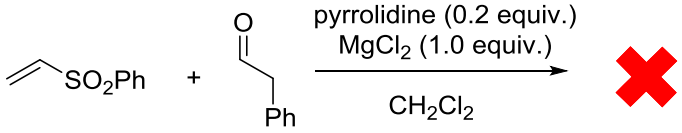
88a-c **5b** **92**

88a: R_1 = H; R_2 = Ph
88b: R_1 = H; R_2 = Me
88c: R_1 = Me; R_2 = CF_3

Entry	Substrate	Equiv. of Aldehyde	Catalyst	Additive	Solvent	T (°C)	Time (h)
1[a]	**88a**	10 equiv.	**XI**	DMA/H_2O (1.0 equiv./2.8 equiv.)	CH_2Cl_2	rt	24
2[b]	**88a**	10 equiv.	**—**	DMA/H_2O (1.0 equiv./2.8 equiv.)	CH_2Cl_2	rt	72
3[a]	**88a**	5.0 equiv.	**XI**	DMA/H_2O (1.0 equiv./2.8 equiv.)	CH_2Cl_2	rt	48
4[a]	**88a**	1.5 equiv.	**XI**	DMA/H_2O (1.0 equiv./2.8 equiv.)	CH_2Cl_2	rt	72

All reactions carried out in a 0.1 mmol scale in the solvent (0.25 M). a) only the cross-aldol product was isolated after the time mentioned. b) only starting materials were observed after the time mentioned.

Changing from isovaleraldehyde to phenylacetaldehyde did not afford the desired product. Instead, the cross-aldol reaction was observed (Table 2.4, entries 1,3 and 4). One additional reaction was performed without adding catalyst to confirm if the aldehyde was reacting with itself, and therefore competing with the Michael addition reaction but no cross-aldol product was observed (Table 2.4, entry 2). This result suggests that the catalyst was in fact condensing with the aldehyde forming the desired enamine which would then react with another molecule of aldehyde which, surprisingly, is more reactive than the sulfone. Therefore, further activation of the sulfone was required in order to observe the desired reactivity. As a proof of this concept a reaction was performed where a Lewis acid ($MgCl_2$) was added to a solution of substrate **86b** in a 1:1 ratio in CH_2Cl_2 (0.5 M) and then a solution of aldehyde (1.5 equiv.) and pyrrolidine (0.2 equiv.) in CH_2Cl_2 (0.5 M) was added dropwise (Scheme 2.10)



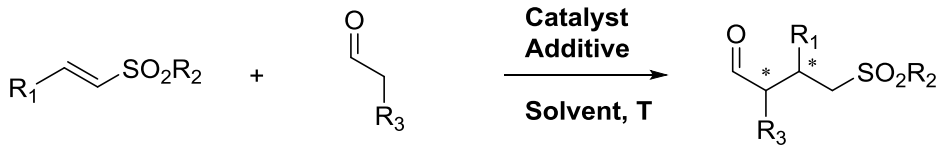
88a (1.0 equiv.) **5b** (1.5 equiv.)

Scheme 2.10 - Attempt to activate sulfone **88a** by the use of a Lewis acid.

This reaction led to a complex mixture as the Lewis acid had very likely coordinated with both sulfone, aldehyde and pyrrolidine making this approach unsuitable for an organocatalytic reaction.

All the results above mentioned pointed out that a more electrophilic sulfone would be required for the reaction to take place, so changing the substituent R_2 from a phenyl or methyl group to a trifluoromethyl group (substrate **88c**) was hoped to lead to the desired Michael addition by providing the necessary electronegatitity to make the sulfone react with the aldehyde in the desired fashion (Table 2.5).

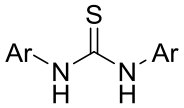
Table 2.5 - Reaction conditions for the organocatalyzed Michael addition of substrate **88c** to aldehyde **5**.



88a-c **5a-b** **92**

88a: R_1 = H; R_2 = Ph
88b: R_1 = H; R_2 = Me
88c: R_1 = Me; R_2 = CF_3

5a: R_3 = *i*-Pr
5b: R_3 = Ph



XX
Ar = 3,5-$(CF_3)_2C_6H_3$

Entry	Substrate	Aldehyde	Catalyst	Additive	Solvent	T (°C)	Time (h)
1[a]	**88c**	**5b**	**XI**	DEA/H_2O (1.0 equiv./2.8 equiv.)	$CDCl_3$	rt	48
2[b]	**88c**	**5a**	**XI**	DEA/H_2O (1.0 equiv./2.8 equiv.)	CH_2Cl_2	rt	48
3[b]	**88c**	**5a**	**IIIb**	**XX**	CH_2Cl_2	rt	48
4[b]	**88c**	**5a**	**IIIa**	**XX**	$CDCl_3$	rt	48
5[b]	**88c**	**5a**	**IIIa**	**XX**	$CDCl_3$	40	24
6[b]	**88c**	**5a**	**IIIa**	**XX**	$CDCl_3$	60	24
7[b]	**88c**	**5a**	**IIIa**	**XX**	Toluene	rt	48
8[b]	**88c**	**5a**	**IIIa**	**XX**	Toluene	40	24
9[b]	**88c**	**5a**	**IIIa**	**XX**	Toluene	60	24
10[b]	**88c**	**5a**	**IIIa**	*o*-FBA	$CDCl_3$	rt	48
11[b]	**88c**	**5a**	**IIIa**	*o*-FBA	$CDCl_3$	40	24
12[b]	**88c**	**5a**	**IIIa**	*o*-FBA	$CDCl_3$	60	24

All reactions carried out in a 0.1 mmol scale in the solvent (0.25 M) with 1.5 equiv. of aldehyde, 0.2 equiv. of catalyst and 0.2 equiv. of additive. a) Decomposition of the starting aldehyde was observed. b) no conversion observed by crude ^{1}H NMR during the time mentioned.

Substrate **88c** was subjected to the same reaction conditions previously described in the presence of catalyst **XI** with both aldehydes **5a** and **5b** but no Michael addition was observed (Table 2.5, entries 1 and 2). It was then decided to use only aldehyde **5a** due to its stability compared to aldehyde **5b** which tends to decompose.

As mentioned in the Introduction section, the squaramide-based aminocatalyst **XI** is more commonly used in dienamine- or trienamine-mediated processes as it contributes to the regioselectivity of the reaction by directing the electrophile, through H-bond, to the more remote positions of the aldehyde.

These results suggest that the squaramide-based aminocatalyst **XI** was not appropriate for an enamine-mediated Michael addition. Thus the catalyst was changed to the TMS-protected diarylprolinol ether **III**.

Since this catalyst does not possess any structural motif that could provide extra activation for the sulfone, it was decided to add a thiourea **XX** as a co-catalyst (Table 2.5, entries 3 to 9). Unfortunately, this system did not result in the desired Michael addition even though different solvents/temperatures were employed. As a final attempt it was added *o*-FBA as an additive (Table 2.5, entries 10 to 12).

This additive would just influence the rate of enamine formation providing the necessary conditions for a faster tautomerization between the iminium-ion, formed upon condensation between the catalyst **III** and aldehyde **5** and the enamine. Thus the additive would assist the condensation itself and therefore guarantee that the enamine was in fact being produced during the reaction and was in fact available to react with the sulfone **88**.

The experiments performed and the conditions explored did not led to the formation of the desired Michael adduct. In the work described by Alexakis *et al.*[50] the fact that the addition took place might be explained by entropic reasons since it was an intramolecular Michael reaction. Deng *et al*.[51] and Zhao and Shi[52] were able to perform the addition to vinyl sulfones just by activating these ones through H-bonding and using highly activated ketones. Therefore, it is clear that even though, the vinyl sulfones are difficult Michael acceptors, the nature and strength of the nucleophile also plays an important role in this reaction as maybe, the enamine did not possessed the nucleophilicity required for the desired Michael addition to take place.

In summary, the addition of simple aldehydes such as isovaleraldehyde or phenylacetaldehyde to vinyl sulfones is a very difficult reaction and further studies in this field should be made in order to discover new catalytic systems that provide the necessary activation of both nucleophile (aldehyde) and electrophile (vinyl sulfone).

Chapter III - Conclusions

In this work two different activation concepts in organocatalysis, the enamine and the tetraenamine activation are presented.

This work corresponds to the first report on the tetraenamine-mediated [4+2]-cycloaddition. This activation method was achieved upon condensation between 2-(cyclohepta-1,3,5-trien-1-yl)acetaldehyde and a TMS-protected diraylprolinol ether catalyst giving the tetraenamine intermediate. This reactive tetraenamine, in the presence of an activated olefin, such as a 3-olefinic oxindole, underwent a [4+2]-cycloaddition reaction resulting in spirocyclic oxindoles bearing four stereocenters and with good to excellent enanteoselectivities (up to >99% ee), excellent diastereoselectivities (86/14 - >95/5 dr) and moderate to good yields (51 - 95%).

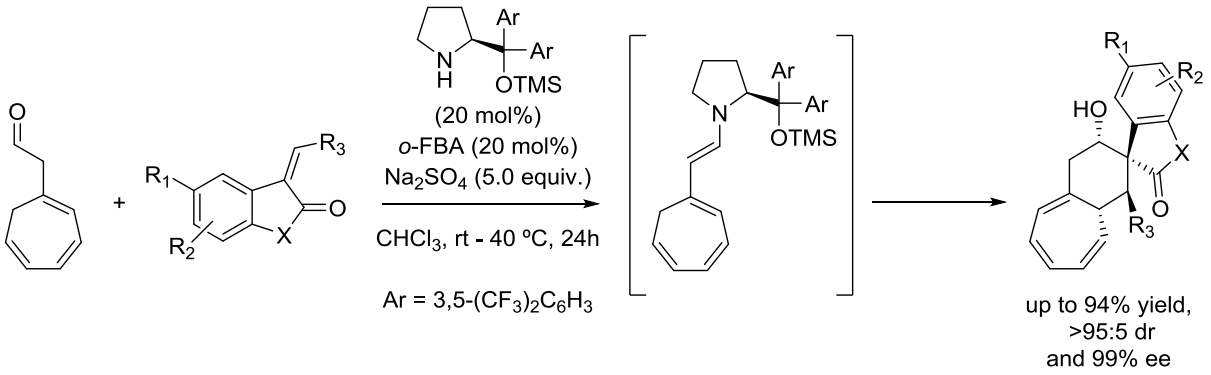
It was also possible to characterize and/or isolate a series of reactive intermediates which gave good insights to a stepwise mechanism via a zwitterionic species. Computational and NMR studies suggest that the [4+2]-cycloaddition takes place through tetraenamine formation, Michael addition to the oxindole, catalyst hydrolysis, cyclization/isomerization sequence.

The synthetic importance of the obtained cycloadduct was highlighted by several transformations preformed in both the six- and seven-membered rings which gave rise, respectivily, to a highly functionalized cyclohexanone and regio- and diastereoselective brominated compound bearing eight stereocenters.

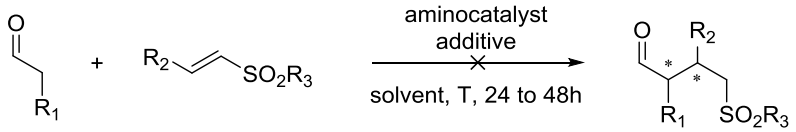
As for the enamine-mediated Michael addition the results were quite disappointing. The main aim in this work was to perform an asymmetric Michael addition between a series of aldehydes and vinyl sulfones. Unfortunately, the sulfones showed to be quite inert under different reaction conditions and catalytic systems. The first attempt made use of a bifunctional squaramide-based aminocatalyst hoping that the H-donors present in the squaramide moiety of this catalyst would provide an extra activation to the sulfone. However, this approach did not led to the formation of the desired adduct. Another catalytic system was then used with a steric shielding aminocatalyst (TMS-protected diarylprolinol ether) and a thiourea as co-catalyst but upon different reaction conditions still no reactivity as observed.

Changes in both the aldehyde and sulfone did not give any satisfactory result which may lead to the need of development of a different catalytic system and/or cooperative catalysis for the Michael addition between these two substrates to take place.

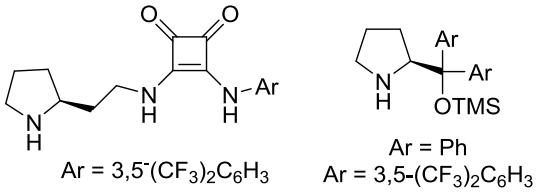
Tetraenamine-mediated [4+2]-cycloaddition



Enamine-mediated Michael addition



Aminocatalysts tested:



Scheme 3.1 - Projects presented in this Master Thesis.

Chapter IV - Experimental Procedure

IV.1 - General Methods

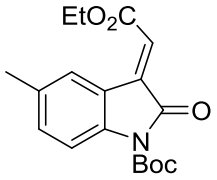
NMR spectra were acquired on a Bruker ARX 400, Varian AS 400 spectrometer or a Bruker AVANCE III HD spectrometer, running at 400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad resonance. ^{13}C NMR spectra were acquired on a broad band decoupled mode.
Mass spectra were recorded on a Bruker MicroTOF-Q High-Performance LC-MS system.
Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation, $KMnO_4$ or *p*-anisaldehyde dip.
For flash chromatography (FC) Iatrobeads (SRS 8060, 60 μm, Mitsubishi Chemical Medience Corporation) or Merck silica gel 60 (230 - 400 mesh) were used.
Optical rotations were measured on a Bellingham+Stanley ADP440+ polarimeter.
The enantiomeric excess (ee) of the products was determined by Ultraperformance Convergence Chromatography (ACQUITY UPC) using Daicel Chiralpak IA, IB, IC and ID columns as chiral stationary phases (columns were kept at 40 °C during measuring).
Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification.
Racemic samples were prepared using a mixture of enantiomers of **IIIa** (20 mol%) in $CHCl_3$.

IV.2 - Experimental procedures for the tetraenamine-mediated [4+2]-cycloaddition

IV.2.1 - General procedures for the synthesis of starting materials

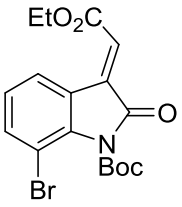
IV.2.1.1 - Synthesis of the olefinic oxindoles 42a - 42n[31]

To a solution of the corresponding isatin (3.4 mmol) in toluene (20 mL) was added the appropriated wittig reagent (3.4 mmol) and the reaction was stirred under reflux until TLC analysis revealed full conversion of the starting material. The reaction mixture was then cooled to rt and the solvent removed under reduced pressure. Without further purification, the crude solid was dissolved in MeCN (25 mL), di-*tert*-butyldicarbonate (3.4 mmol) and DMAP (3.0 mmol) were added. The mixture was allowed to stir at rt until TLC analysis confirmed full conversion of the starting material.
The solvent was removed under reduced pressure and the mixture was purified by FC to yield the desired products (see details below).
For a descriptive procedure of compound **42l** see below.
Compound **42m** was synthesized using commercially available 1-benzothiophene-2,3-dione as starting material and was obtained after the wittig olefination step.
The remaining oxindole derivatives were already available from previous projects.



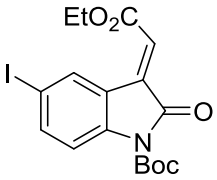
42d

***tert* - butyl (*E*) - 3 - (2 - ethoxy - 2 - oxoethylidene) - 5 - methyl - 2 - oxoindoline - 1 - carboxylate (42d)** was isolated by FC on silica (pentane/EtOAc 10:1) in 40% yield over two steps.
Yellow solid. **Mp**: 123.3 - 124.3 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (m, 1H, Ar-*H*), 7.78 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.24 (dd, *J* = 8.5, 1.3 Hz, 1H, Ar-*H*), 6.89 (s, 1H, C=C*H*), 4.33 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.38 (s, 3H, Ar-CH_3), 1.64 (s, 9H, $C(CH_3)_3$), 1.38 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.9 (*C*=O), 165.5 (*C*=O), 148.8 (*C*=O), 139.7 (Ar-*C*), 136.6 (*C*=CH), 134.2 (Ar-*C*), 133.4 (Ar-*C*H), 128.6 (Ar-*C*H), 122.8 (C=*C*H), 120.1 (Ar-*C*), 114.7 (Ar-*C*H), 84.6 ($C(CH_3)_3$), 61.3 (OCH_2CH_3), 28.1 (3C, $C(CH_3)_3$), 21.1 (Ar-CH_3), 14.2 (OCH_2CH_3). **HRMS** (ESI+) *m*/*z* calcd. for $C_{18}H_{21}NO_5Na$ $[M+Na]^+$: 354.1317; found: 354.1314.



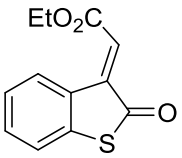
42h

***tert* - butyl (*E*) - 7 - bromo - 3 - (2 - ethoxy - 2 - oxoethylidene) - 2 - oxoindoline - 1 - carboxylate (42h)** was isolated by FC on silica (pentane/EtOAc 20:1) in 12% yield over two steps.
Pale orange solid. **Mp**: 67.7 - 69.7 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.57 (d, *J* = 8.1 Hz, 1H, Ar-*H*), 7.07 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 6.92 (s, 1H, C=C*H*), 4.33 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 1.65 (s, 9H, $C(CH_3)_3$), 1.37 (dd, *J* = 9.5, 4.7 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6 (*C*=O), 165.3 (*C*=O), 147.9 (*C*=O), 140.7 (Ar-*C*Br), 137.4 (Ar-*C*H), 136.5 (Ar-*C*), 127.8 (Ar-*C*H), 125.9 (Ar-*C*H), 125.0 (C=*C*H), 123.7 (*C*=CH), 107.1 (Ar-*C*H), 86.2 ($C(CH_3)_3$), 61.9 (OCH_2CH_3), 28.0 (3C, $C(CH_3)_3$), 14.4 (OCH_2CH_3). **HRMS** (ESI+) *m*/*z* calcd. for $C_{17}H_{18}BrNO_5Na$ $[M+Na]^+$: 418.0266; found: 418.0268.



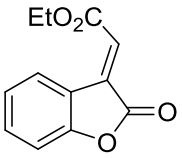
42i

***tert* - butyl (*E*) - 3 - (2 - ethoxy - 2 - oxoethylidene) - 5 - iodo - 2 - oxoindoline - 1 - carboxylate (42i)** was isolated by FC on silica (pentane/EtOAc 10:1) in 70% yield over two steps.
Yellow solid. **Mp**: 99.4 - 101.0 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 1.7 Hz, 1H, Ar-*H*), 7.74 (dd, *J* = 8.6, 1.8 Hz, 1H, Ar-*H*), 7.69 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 6.91 (s, 1H, C=C*H*), 4.35 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 1.63 (s, 9H, $C(CH_3)_3$), 1.39 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.0 (*C*=O), 164.8 (*C*=O), 148.6 (*C*=O), 141.4 (Ar-*C*I), 141.18 (Ar-*C*H), 136.8 (Ar-*C*H), 135.0 (*C*=CH), 124.6 (C=*C*H), 122.0 (Ar-*C*), 116.9 (Ar-*C*H), 88.0 (Ar-*C*), 85.1 ($C(CH_3)_3$), 61.6 (OCH_2CH_3), 28.0 (3C, $C(CH_3)_3$), 14.1 (OCH_2CH_3). **HRMS** (ESI+) *m*/*z* calcd. for $C_{17}H_{18}INO_5Na$ $[M+Na]^+$: 466.0127; found: 466.0124.



42m

ethyl (*E*)-2-(2-oxobenzo[b]thiophen-3(2*H*)-ylidene)acetate (42m) was isolated by FC on silica (pentane/EtOAc 4:1) in 94% yield.
Orange Solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.60 (m, 1H, Ar-*H*), 7.46 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 7.29 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.03 (s, 1H, C=C*H*), 4.33 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 1.36 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).

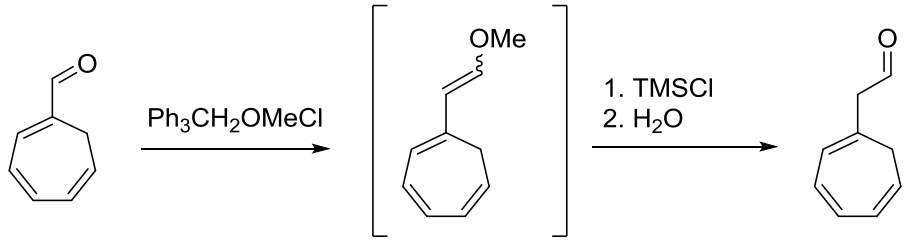


42l

ethyl (*E*)-2-(2-oxobenzofuran-3(2H)-ylidene)acetate (42l): To a solution of benzofuran-2(3*H*)one (1g, 7.46 mmol, 1.0 equiv.) in dry toluene (20 mL) was added ethyl glyoxalate solution (50% in toluene, 1.55 mL, 7.83 mmol, 1.05 equiv.) and triethylamine (155.9 µL, 1.12 mmol, 0.15 equiv.). The mixture was stirred under reflux conditions until TLC analysis indicated full conversion of the starting material. The reaction mixture was then poured into cold water (40 mL) and extracted with Et_2O (3x20 mL), the layers were separated and the organic phase was washed with water (4x12 mL) and dried with Na_2SO_4. FC on silica (pentane/EtOAc 10:1) afforded the pure product in 40% yield as a yellow solid. **Mp**: 84.7 - 85.4 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 7.48 (td, *J* = 8.0, 1.2 Hz, 1H, Ar-*H*), 7.22 (t, *J* = 7.7 Hz, 1H, Ar-*H*), 7.14 (d, *J* = 8.1 Hz, 1H, Ar-*H*), 6.93 (s, 1H, C=C*H*), 4.35 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 1.38 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.7 (*C*=O), 1649 (*C*=O), 156.1 (Ar-*C*), 133.8 (Ar-*C*), 133.5 (Ar-*C*H), 128.9 (Ar-*C*H), 125.4 (C=*C*H), 124.6 (Ar-*C*H), 120.6 (*C*=CH), 111.0 (Ar-*C*H), 61.6 (OCH_2CH_3), 14.1 (OCH_2CH_3). **HRMS** (ESI+) *m*/*z* calcd. for $C_{12}H_9O_4Na$ $[M+Na]^+$: 241.0471; found: 241.0469.

IV.2.1.2 - Synthesis of 2-(cyclohepta-1,3,5-trien-1-yl)acetaldehyde (75)

Aldehyde **93** was prepared according to literature procedure in 15 g scale[54].



93 **94** **75**

E/Z = 1/1

A solution of (methoxymethyl)triphenylphosphonium chloride (20.3 g, 59.3 mmol, 1.3 equiv.) in dry THF (180 mL) was cooled to 0 °C under Argon and a *n*BuLi solution (1.6 M in hexane, 35.6 mL, 57.0 mmol, 1.25 equiv.) was added dropwise. The mixture was stirred for 2 h at 0 °C. A solution of aldehyde **93** (5.5 g, 45.6 mmol, 1.0 equiv.) in THF (40 mL) was added dropwise. After full addition, the reaction mixture was warmed to rt and stirred for further 12 h. After full conversion of aldehyde (TLC) the reaction mixture was poured into cold pentane (300 mL, −78 °C). The crude mixture was filtrated over Celite and sand and the filtrate was washed with a 1:1 mixture of pentane:Et_2O (500 mL, −20 °C) . The solvent was evaporated carefully (product **94** is volatile!). The crude product **90** was used for the next step without further purification.

A solution of crude product **94** in dry CH_2Cl_2 (50 mL) was cooled to 0 °C under Argon and TMSCl (17.0 mL, 136.8 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was stirred for 15 min at 0 °C and further 2 h at rt. Then the reaction mixture was cooled to 0 °C again and H_2O (8.0 mL, 456.0 mmol, 10 equiv.) was added dropwise. After 45 min H_2O (250 mL) and sat. $NaHCO_3$ solution (60 mL) were added at 0 °C. After extraction with CH_2Cl_2 (3 x 100 mL) the combined organic layers were dried with Na_2SO_4 and the solvent was evaporated. FC on Iatrobeats (pentane:CH_2Cl_2 4:1 to 2:1) afforded the pure aldehyde **75** in 40% yield over 2 steps. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.60 (t, *J* = 2.3 Hz, 1H, C*H*O), 6.56 (m, 2H), 6.20 (m, 1H), 6.09 (d, *J* = 5.2 Hz, 1H), 5.40 (m, 1H), 3.36 (m,

2H), 2.31 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.8 (*C*=O), 130.7, 130.2, 127.1, 125.9, 124.9, 120.4, 53.1, 32.5. **HRMS** (APCI+) *m*/*z* calcd. for $C_9H_{11}O$ $[M+H]^+$: 135.0804; found: 135.0801.

IV.2.2 - General Procedure for the Synthesis of the Cycloadducts 77a-n

In a dry glass vial, a mixture of the oxindole **42** (0.10 mmol), *o*-FBA (0.02 mmol), catalyst **IIIa** (0.02 mmol) and Na_2SO_4 (0.5 mmol) was dissolved in 0.4 mL of dry $CHCl_3$ before aldehyde **75** (0.12 mmol) was added. The reaction mixture was brought to the appropriate temperature and stirred for the time indicated. When the reaction was completed, the mixture was plugged over Iatrobeads, concentrated and purified by FC on Iatrobeads to afford the corresponding cycloadduct.

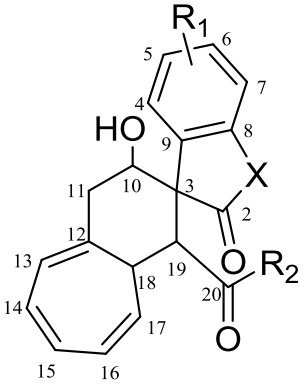
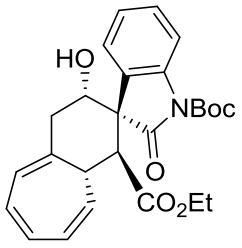


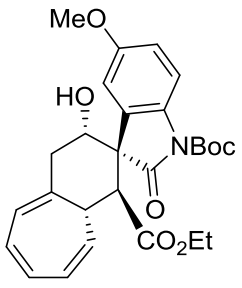
Figure 4.1 - Labeling of hydrogen and carbon atoms for the cycloadducts **77a-n**.



77a

Cycloadduct **77a** was obtained after 24 h at 40 °C. FC on Iatrobeads (pentane:EtOAc 15:1 to 10:1) afforded the pure compound in 93% yield, >95:5 dr and 94% ee.

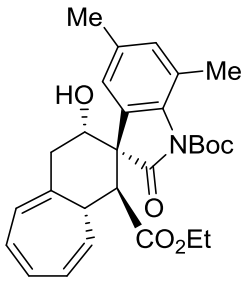
Yellow foam. $[\alpha]_D^{20}$ = −14.6 (*c* 0.51, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 1H, Ar-*H*), 7.29 (m, 1H, Ar-*H*), 7.09 (m, 2H, Ar-*H*), 6.65 (m, 2H, H^{14+15}), 6.20 (m, 2H, H^{13+16}), 5.05 (dd, *J* = 9.2, 5.0 Hz, 1H, H^{17}), 4.03 (m, 1H, H^{10}), 3.96 (d, *J* = 10.3 Hz, 1H, H^{19}), 3.71 (m, 2H, OCH_2CH_3), 3.12 (m, 1H, -O*H*), 2.99 (dd, *J* = 16.2, 7.6 Hz, 1H, H^{11a}), 2.76 (dd, *J* = 16.4, 3.8 Hz, 1H, H^{11b}), 2.51 (dd, *J* = 10.2, 4.9 Hz, 1H, H^{18}), 1.66 (s, 9H, $C(CH_3)_3$), 0.86 (t, *J* = 7.1, 3H, OCH_2CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.0 (*C*=O), 170.9 (*C*=O), 149.1 (*C*=O), 140.3 (Ar-*C*), 131.1 (C^{12}), 130.5 (C^{15}), 130.0 (C^{14}), 128.9 (Ar-*C*H), 128.5 (Ar-*C*), 125.6 (C^{17}), 125.0 (C^{16}), 124.8 (Ar-*C*H), 124.2 (Ar-*C*H), 122.7 (C^{13}), 115.0 (Ar-*C*H), 84.6 ($C(CH_3)_3$), 73.9 (*C*-OH), 61.0 (OCH_2CH_3), 55.5 (C^3), 49.7 (C^{19}), 36.7 (C^{18}), 35.6 (C^{11}), 28.1 (3C, $C(CH_3)_3$), 13.3 (OCH_2CH_3). **HRMS** (ESI+) *m*/*z* calcd. for $C_{26}H_{29}NO_6Na$ $[M+Na]^+$: 474.1887; found: 474.1889. **UPC^2**: IC, CO_2/MeOH 80/20, 3.0 mL·min^{-1}; t_{major} = 1.7 min; t_{minor} = 2.4 min.



77b

Cycloadduct **77b** was obtained after 24 h at 40 °C. FC on Iatrobeads (pentane:EtOAc 10:1 to 5:1) afforded the pure compound in 84% yield, >95:5 dr and 91% ee.

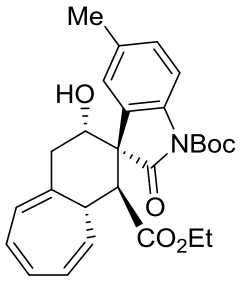
Yellow oil. $[\alpha]_D^{20}$ = −37.8 (*c* 0.66, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.9 Hz, 1H), 6.81 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.70 (d, *J* = 2.6 Hz, 1H) 6.65 (dd, *J* = 10.0, 4.6 Hz, 1H), 6.21 (m, 2H), 5.08 (dd, *J* = 9.2, 5.1 Hz, 1H), 4.04 (dd, *J* = 6.9, 4.3 Hz, 1H), 3.98 (d, *J* = 10.2 Hz, 1H), 3.77 (m, 2H), 3.72 (s, 3H), 2.99 (dd, *J* = 16.5, 7.0 Hz, 1H), 2.81 (dd, *J* = 16.8, 3.8 Hz, 1H), 2.47 (m, 1H), 1.66 (s, 9H), 0.88 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.2, 170.9, 156.8, 149.0, 133.5, 130.8, 130.5, 130.0, 129.5, 125.7, 125.0, 122.6, 115.6, 113.3, 110.9, 84.5, 73.4, 61.0, 55.6, 55.5, 49.6, 36.7, 35.3, 28.1 (3C), 13.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{27}H_{31}NO_7Na$ $[M+Na]^+$: 504.1993; found: 504.1991. **UPC^2**: IC, CO_2/MeOH 80/20, 3.0 mL·min^{-1}; t_{major} = 1.9 min; t_{minor} = 2.9 min.



77c

Cycloadduct **77c** was obtained after 24 h at 40 °C. FC on Iatrobeads (pentane:EtOAc 10:1) afforded the pure compound in 66% yield, >95:5 dr and 95% ee.

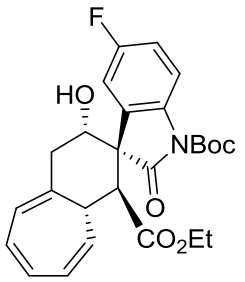
Yellow oil. $[\alpha]_D^{20}$ = −30.0 (*c* 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.72 (s, 1H), 6.65 (m, 2H), 6.19 (m, 2H), 5.03 (dd, *J* = 9.2, 4.9 Hz, 1H), 4.00 (dd, *J* = 7.9, 3.8 Hz, 1H), 3.93 (d, *J* = 10.4 Hz, 1H), 3.79 (q, *J* = 7.1 Hz, 2H), 3.00 (dd, *J* = 15.8, 8.1 Hz, 2H), 2.74 (dd, *J* = 16.0, 3.7 Hz, 1H), 2.54 (dd, *J* = 10.3, 4.0 Hz, 1H), 2.23 (s, 3H), 2.20 (s, 3H), 1.65 (s, 9H), 0.82 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.7, 170.9, 149.1, 136.4, 134.2, 132.4, 131.6, 130.4, 129.9, 129.7, 125.6, 125.0, 123.2, 122.5, 122.2, 84.7, 74.3, 61.1, 55.9, 49.6, 36.6, 35.7, 27.8 (3C), 21.0, 19.5, 13.3. **HRMS** (ESI+) *m*/*z* calcd. for $C_{28}H_{33}NO_6Na$ $[M+Na]^+$: 502.2200; found: 502.2208. **UPC^2**: IC, CO_2/MeOH 80/20, 3.0 mL·min^{-1}; t_{major} = 1.4 min; t_{minor} = 1.5 min.



77d

Cycloadduct **77d** was obtained after 24 h at 40 °C. FC on Iatrobeads (pentane:EtOAc 15:1 to 10:1) afforded the pure compound in 86% yield, >95:5 dr and 84% ee.

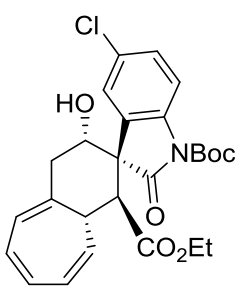
Yellow oil. $[\alpha]_D^{20}$ = −7.8 (*c* 0.49, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.88 (s, 1H), 6.65 (m, 2H), 6.21 (m, 2H), 5.03 (dd, *J* = 9.2, 4.9 Hz, 1H), 4.03 (br s, 1H), 3.95 (d, *J* = 10.5 Hz, 1H), 3.73 (m, 2H), 3.01 (dd, *J* = 16.0, 8.0 Hz, 2H), 2.75 (dd, *J* = 16.0, 3.7 Hz, 1H), 2.47 (dd, *J* = 10.3, 4.3 Hz, 1H), 2.26 (s, 3H), 1.66 (s, 9H), 0.88 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.1, 170.8, 149.1, 137.9, 134.4, 131.4, 130.5, 130.0, 129.4, 128.5, 125.5, 125.0, 124.6, 122.6, 114.7, 84.4, 74.3, 60.9, 55.6, 49.9, 36.6, 35.9, 28.1 (3C), 21.1, 13.3. **HRMS** (ESI+) *m*/*z* calcd. for $C_{27}H_{31}NO_6Na$ $[M+Na]^+$: 488.2044; found: 488.2045. **UPC^2**: IC, CO_2/MeOH 80/20, 3.0 mL·min^{-1}; t_{major} = 1.5 min; t_{minor} = 2.2 min.



77e

Cycloadduct **77e** was obtained after 24 h at rt. FC on Iatrobeads (pentane:EtOAc 15:1 to 10:1) afforded the pure compound in 80% yield, 94:6 dr and 93% ee.

Yellow oil. $[\alpha]_D^{20}$ = −1.6 (*c* 0.49, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 9.0, 4.6 Hz, 1H), 7.01 (td, *J* = 8.9, 2.7 Hz, 1H), 6.85 (dd, *J* = 7.9, 2.7 Hz, 1H), 6.67 (m, 2H), 6.20 (m, 2H), 5.07 (dd, *J* = 9.2, 5.0 Hz, 1H), 4.04 (m, 1H), 3.98 (d, *J* = 10.4 Hz, 1H), 3.77 (m, 2H), 3.04 (m, 2H), 2.78 (dd, *J* = 16.5, 4.1 Hz, 1H), 2.44 (ddd, *J* = 10.3, 5.0, 1.2 Hz, 1H), 1.66 (s, 9H), 0.89 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) 177.6, 170.7, 160.1 (d, *J* = 244.3 Hz), 158.6, 148.9, 136.3 (d, *J* = 2.9 Hz), 130.6, 130.3, 130.2 (d, *J* = 8.1 Hz), 130.0, 125.2, 122.9, 116.3 (d, *J* = 8.1 Hz), 115.4 (d, *J* = 22.7 Hz), 111.7 (d, *J* = 24.9 Hz), 84.9, 73.7, 61.1, 55.7, 49.5, 36.7, 35.5, 28.1 (3C), 13.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{26}H_{28}FNO_6Na$ $[M+Na]^+$: 492.1793; found: 492.1796. **UPC^2**: IC, CO_2/MeOH 80/20, 3.0 mL·min^{-1}; t_{major} = 1.3 min; t_{minor} = 1.8 min.

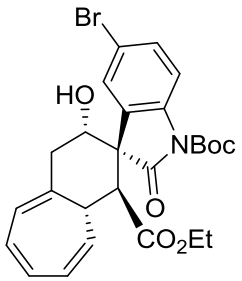


77f

Cycloadduct **77f** was obtained after 24 h at rt. FC on Iatrobeads (pentane:EtOAc 14:1 to 10:1) afforded the pure compound in 71% yield, 88:12 dr and 95% ee.

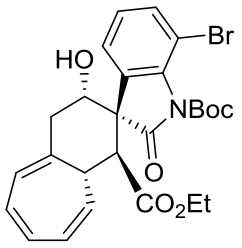
Yellow solid. $[\alpha]_D^{20}$ = −20.6 (*c* = 0.5, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.7 Hz, 1H), 7.28 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.07 (d, *J* = 2.1 Hz, 1H), 6.69 (m, 2H), 6.22 (m, 2H), 5.04 (dd, *J* = 9.3, 5.0 Hz, 1H), 4.04 (m, 1H), 3.97 (d, *J* = 10.8 Hz, 1H), 3.78 (m, 2H), 3.02 (m, 1H), 2.90 (d, *J* = 5.6 Hz, 1H), 2.76 (m, 1H), 2.45 (m, 1H), 1.66 (s, 9H), 0.89 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.1, 170.5, 148.8, 138.9, 130.7, 130.6, 130.6, 130.1, 130.0, 129.0, 125.2, 125.1, 124.2, 122.9, 116.2, 85.0, 74.2, 61.1, 55.7, 49.8, 36.6, 35.9, 28.1 (3C), 13.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{26}H_{28}ClNNaO_6Na$ $[M+Na]^+$: 508.1497; found: 508.1502. **UPC^2**: IC, CO_2/MeOH 80/20,

3.0 mL·min^{-1}; t_{major} = 1.6 min; t_{minor} = 2.2 min.



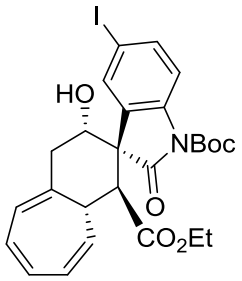
77g

Cycloadduct **77g** was obtained after 24 h at rt. FC on Iatrobeads (pentane:EtOAc 15:1 to 10:1) afforded the pure compound in 93% yield, 89:11 dr and 95% ee. Yellow oil. $[\alpha]_D^{20}$ = −17.2 (*c* 0.69, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.7 Hz, 1H), 7.43 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.20 (d, *J* = 2.0 Hz, 1H), 6.67 (m, 2H), 6.22 (m, 2H), 5.03 (dd, *J* = 9.3, 4.9 Hz, 1H), 4.04 (m, 1H), 3.97 (d, *J* = 10.9 Hz, 1H), 3.77 (m, 2H), 3.02 (dd, *J* = 15.8, 8.5 Hz, 1H), 2.88 (d, *J* = 5.7 Hz, 1H), 2.74 (dd, *J* = 15.8, 3.8 Hz, 1H), 2.44 (dd, *J* = 11.3, 4.3 Hz, 1H), 1.65 (s, 9H), 0.88 (t, *J* = 7.1, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.9, 170.5, 148.8, 139.4, 131.9, 131.0, 130.7, 130.0, 126.9, 125.9, 125.1, 125.1, 122.8, 117.6, 116.6, 85.0, 74.4, 61.1, 55.6, 49.9, 36.6, 36.0, 28.1 (3C), 13.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{26}H_{28}BrNO_6Na$ $[M+Na]^+$: 552.0992; found: 552,0988. **UPC^2**: IC, CO_2/MeOH 80/20, 3.0 mL·min^{-1}; t_{major} = 1.6 min; t_{minor} = 2.5 min.



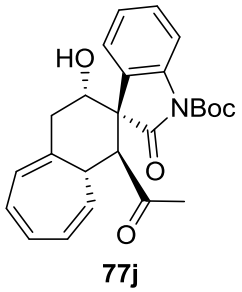
77h

Cycloadduct **77h** was obtained after 24 h at rt. FC on Iatrobeats (pentane:EtOAc 12:1) afforded the pure compound in 72% yield, >95:5 dr and 95% ee. Yellow oil. $[\alpha]_D^{20}$ = +6.2 (*c* 0.47, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.1 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.95 (t, *J* = 7.8 Hz, 1H), 6.64 (m, 2H), 6.20 (m, 2H), 5.04 (dd, *J* = 9.2, 5.0 Hz, 1H), 4.03 (dd, *J* = 7.6, 4.1 Hz, 1H), 3.95 (d, *J* = 10.3 Hz, 1H), 3.82 (m, 2H), 3.00 (dd, *J* = 16.2, 7.6 Hz, 1H), 2.74 (dd, *J* = 16.4, 3.8 Hz, 1H), 2.50 (dd, *J* = 10.0, 4.6 Hz, 1H), 1.67 (s, 9H), 0.85 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.9, 170.6, 147.7, 139.1, 133.6, 132.7, 130.7, 130.5, 129.9, 125.6, 125.4, 125.1, 123.2, 122.7, 106.4, 85.6, 73.7, 61.3, 56.3, 49.1, 36.5, 35.4, 27.7 (3C), 13.3. **HRMS** (ESI+) *m*/*z* calcd. for $C_{26}H_{28}BrNO_6Na$ $[M+Na]^+$: 552.0992; found: 552,0973. **UPC^2**: IC, CO_2/i-PrOH 90/10, 3.0 mL·min^{-1}; t_{major} = 2.1 min; t_{minor} = 2.6 min.



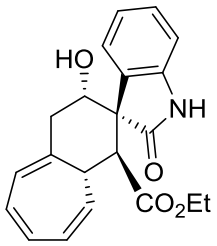
77i

Cycloadduct **77i** was obtained after 24 h at rt. FC on Iatrobeads (pentan:/EtOAc 15:1 to 10:1) afforded the pure compound in 77% yield, 86:14 dr and 93% ee. Yellow solid. $[\alpha]_D^{20}$ = −40.4 (*c* = 0.5, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.37 (d, *J* = 1.7 Hz, 1H), 6.68 (m, 2H), 6.22 (m, 2H), 5.03 (dd, *J* = 9.3, 4.9 Hz, 1H), 4.04 (dd, *J* = 8.6, 4.1 Hz, 1H), 3.96 (d, *J* = 10.9 Hz, 1H), 3.78 (qd, *J* = 7.1, 5.2 Hz, 2H), 3.02 (dd, *J* = 15.9, 8.6 Hz, 1H), 2.82 (s, 1H), 2.73 (dd, *J* = 15.9, 4.0 Hz, 1H), 2.44 (m, 1H), 1.65 (s, 9H), 0.88 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.7, 170.4, 148.8, 140.2, 137.9, 132.6, 131.4, 130.8, 130.7, 123.0, 125.1, 125.1, 122.8, 116.9, 88.0, 85.0, 74.5, 61.1, 55.5, 50.0, 36.68, 36.1, 28.1 (3C), 13.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{26}H_{28}INO_6Na$ $[M+Na]^+$: 600.0854; found: 600.0855. **UPC^2**: IC, CO_2/MeOH 80/20, 3.0 mL·min^{-1}; t_{major} = 1.9 min; t_{minor} = 3.1 min.



77j

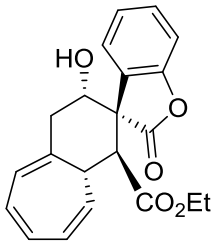
Cycloadduct **77j** was obtained after 24 h at rt. FC on Iatrobeads (pentane:EtOAc 14:1 to 10:1) afforded the pure compound in 51% yield, >95:5 dr and 87% ee. Yellow solid. $[\alpha]_D^{20}$ = −10.8 (*c* = 0.5, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.1 Hz, 1H), 7.30 (td, *J* = 7.9, 1.4 Hz, 1H), 7.10 (m, 2H), 6.73 (m, 2H), 6.34 (dd, *J* = 9.1, 4.9 Hz, 1H), 6.27 (m, 1H), 5.30 (dd, *J* = 9.1, 5.6 Hz, 1H), 4.08 (d, *J* = 10.0 Hz, 1H), 3.94 (t, *J* = 4.2 Hz, 1H), 2.96 (m, 2H), 2.05 (m, 1H), 1.96 (s, 3H), 1.67 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.9, 179.2, 148.9, 140.3, 130.6, 130.6, 123.0, 128.6, 127.8, 125.5, 125.5, 124.5, 124.1, 122.9, 115.3, 84.8, 70.8, 56.7, 37.7, 37.6, 33.8, 28.1 (3C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{25}H_{27}NO_5Na$ $[M+Na]^+$: 444.1781; found: 444.1778. **UPC^2**: IC, CO_2/MeOH 80/20, 3.0 mL·min^{-1}; t_{minor} = 2.5 min; t_{major} = 3.1 min.



77k

Cycloadduct **77k** was obtained after 24 h at 40 °C. FC on Iatrobeads (pentane:EtOAc 3:1 to 2:1) afforded the pure compound in 71% yield, >95:5 dr and 89% ee.

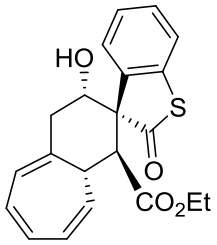
Yellow foam. $[\alpha]_D^{20}$ = −7.1 (*c* =0.5, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.23 (td, *J* = 7.8, 1.1 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.98 (td, *J* = 7.6, 1.0 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.67 (t, *J* = 3.2 Hz, 2H), 6.21 (m, 2H), 5.16 (dd, *J* = 9.3, 5.3 Hz, 1H), 4.01 (t, *J* = 5.1 Hz, 1H), 3.97 (d, *J* = 9.5 Hz, 1H), 3.82 (m, 2H), 3.70 (m, 1H), 2.93 (m, 2H), 2.47 (m, 1H), 0.87 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.5, 171.5, 141.0, 130.7, 130.2, 130.1, 129.2, 128.8, 126.0, 125.3, 124.9, 123.0, 122.6, 110.0, 71.7, 61.0, 55.0, 48.0, 37.0, 34.7, 13.6. **HRMS** (ESI+) *m*/*z* calcd. for $C_{21}H_{21}NO_4Na$ $[M+Na]^+$: 374.1363; found: 374.1358. **UPC^2**: IC, CO_2/MeOH 80/20, 3.0 mL·min^{-1}; t_{minor} = 4.0 min; t_{major} = 4.4 min.



77l

Cycloadduct **77l** was obtained after 24 h at 40 °C. FC on Iatrobeats (pentane:EtOAc 6:1) afforded the pure compound in 59% yield >95:5 dr and 64% ee.

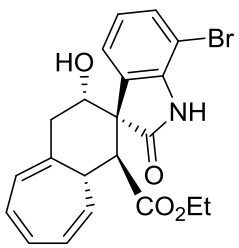
Yellow oil. $[\alpha]_D^{20}$ = −19.6 (*c* 0.70, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (m, 1H), 7.14 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.09 (td, *J* = 7.5, 0.8 Hz, 1H), 6.66 (m, 2H), 6.23 (m, 2H), 5.10 (dd, *J* = 9.2, 5.1 Hz, 1H), 4.11 (m, 1H), 3.98 (d, *J* = 10.4 Hz, 1H), 3.81 (q, *J* = 7.1 Hz, 2H), 3.00 (dt, *J* = 15.8, 7.9 Hz, 1H), 2.93 (d, *J* = 3.3 Hz, 1H), 2.83 (dd, *J* = 16.6, 3.9 Hz, 1H), 2.45 (m, 1H), 0.89 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.6, 170.7, 153.7, 130.6, 130.3, 129.9, 129.7, 127.6, 125.2, 125.1, 124.7 (2C), 122.9, 110.7, 73.2, 61.3, 54.7, 49.2, 36.7, 35.2, 13.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{21}H_{20}O_5Na$ $[M+Na]^+$: 375.1208; found: 375,1202. **UPC^2**: IC, CO_2/MeOH 80/20, 3.0 mL·min^{-1}; t_{major} = 2.1 min; t_{minor} = 2.4 min.



77m

Cycloadduct **77m** was obtained after 24 h at 40 °C. FC on Iatrobeads (pentane:EtOAc 10:1) afforded the pure compound in 75% yield, >95:5 dr and 50% ee.

Yellow oil. $[\alpha]_D^{20}$ = +5.4 (*c* 0.73, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.7 Hz, 1H), 7.57 (dt, *J* = 8.1, 3.3 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.26 (m, 2H), 6.65 (m, 2H), 6.22 (dt, *J* = 13.8, 6.9 Hz, 1H), 6.13 (s, 1H), 5.30 (dd, *J* = 9.0, 5.6 Hz, 1H), 4.24 (d, *J* = 9.6 Hz, 1H), 4.12 (dd, *J* = 6.2, 2.1 Hz, 1H), 3.91 (m, 2H), 3.07 (dd, *J* = 18.6, 6.3 Hz, 1H), 2.88 (d, *J* = 18.6, Hz, 1H), 2.21 (dd, *J* = 8.5, 5.9 Hz, 1H), 0.86 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.1, 171.5, 151.7, 136.0, 130.2, 130.1, 127.7, 126.9, 125.5, 125.1, 124.7, 123.9, 123.0, 70.8, 65.6, 61.2, 47.6, 40.1, 36.2, 29.7, 13.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{21}H_{20}O_4SNa$ $[M+Na]^+$: 391.0975; found: 391.0979. **UPC^2**: IC, CO_2/MeOH 80/20, 3.0 mL·min^{-1}; t_{minor} = 2.8 min; t_{major} = 3.4 min.

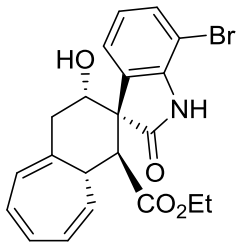


77n

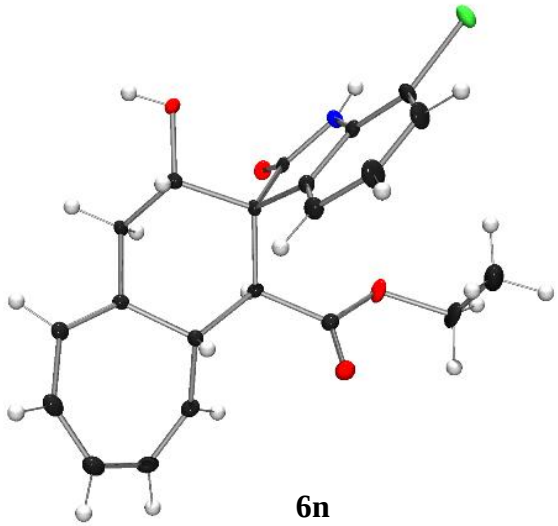
Cycloadduct **77n** was obtained after 24 h at rt. FC on Iatrobeads (pentane:EtOAc 8:1 to 4:1) afforded the pure compound in 74% yield, >95:5 dr and 89% ee (>99.5% ee after crystallization).

Yellow solid. $[\alpha]_D^{20}$ = −26.2 (*c* 0.53, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.9 Hz, 1H), 6.67 (m, 2H), 6.22 (m, 2H), 5.13 (dd, *J* = 9.2, 5.2 Hz, 1H), 4.00 (m, 1H), 3.95 (d, *J* = 9.9 Hz, 1H), 3.84 (m, 2H), 3.59 (d, *J* = 3.6 Hz, 1H) 2.99 (dd, *J* = 17.0, 6.0 Hz, 1H), 2.82 (dd, *J* = 17.0, 4.7 Hz, 1H), 2.47 (m, 1H), 0.88 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 180.2, 171.2, 140.7, 131.4, 130.8, 130.5, 130.4, 130.0, 125.7, 125.0, 124.1, 123.9, 122.7, 103.0, 72.2, 61.0, 56.3, 48.2, 36.9, 34.9, 13.5. **HRMS** (ESI+) *m*/*z* calcd. for $C_{21}H_{20}BrNO_4Na$ $[M+Na]^+$: 452.0468; found: 452.0466. **UPC^2**: IC, CO_2/MeOH 80/20, 3.0 mL·min^{-1}; t_{minor} = 3.8 min; t_{major} = 4.6 min.

IV.2.3 - X-Ray structure of cycloadduct 77n



77n

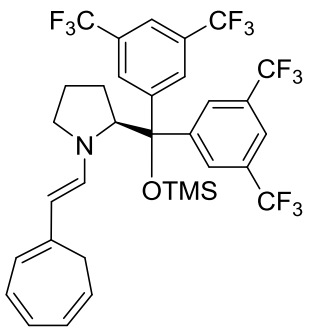


6n

Crystal data for [**1**]: $C_{21}H_{20}BrNO_4$, M = 430.29, monoclinic, Space group P 1 21 1 (no. 6), a = 10.3326(5) Å, b = 6.3617(3) Å, c = 14.1521(7) Å, β = 96.731(2)°, V = 923.85(8) Å^3, T = 100 K, Z = 2, d_c = 1.547 g cm^{-3}, μ(Mo Kα, λ = 0.56086 Å) = 1.213 mm^{-1}, 13541 reflections collected, 5045 unique [R_{int} = 0.0341], which were used in all calculations. Refinement on F^2, final R(F) = 0.0384, R_w(F2) = 0.0774.

IV.2.4 - Synthesis of intermediates 76, 78 and product 82

IV.2.4.1 - Tetraenamine 76



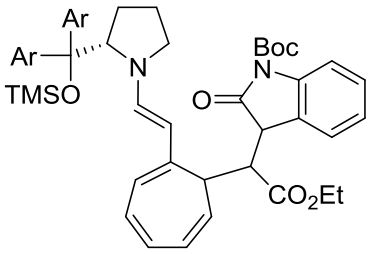
76

In a NMR tube aldehyde **5** (0.10 mmol, 1.0 equiv.) and catalyst **IIIa** (Ar = 3,5-$(CF_3)_2C_6H_3$, 0.10 mmol, 1.0 equiv.) or catalyst **IIIb** (Ar = Ph, 0.10 mmol, 1.0 equiv.) were dissolved in 0.4 mL of $CDCl_3$ and molecular sieves (4 Å) were added. The reaction mixture was shaken for 15 min to obtain **76** as a crude product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (m, 2H), 7.91 (m, 4H), 6.8 (d, *J* = 13.7 Hz, 1H), 6.47 (dd, *J* = 11.0, 6.3 Hz, 1H), 6.27 (dd, *J* = 11.0, 5.5 Hz, 1H), 6.18 (dd, *J* = 9.2, 5.5 Hz, 1H), 5.86 (d, *J* = 6.3 Hz, 1H), 5.21 (m, 1H), 5.14 (d, *J* = 13.7 Hz, 1H), 4.59 (dd, *J* = 9.2, 1.9 Hz, 1H), 2.92 (m, 1H), 2.45 (m, 2H), 2.31 (m, 1H), 2.23 (m, 1H), 1.83 (m, 1H), 1.61 (m, 1H), 0.42 (m, 1H), 0.11 (m, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.5, 143.5, 138.1, 132.9, 131.7 (q, *J* = 34 Hz, 2C), 131.5 (q, *J* = 34 Hz, 2C), 131.3, 129.3 (m, 2C), 129.2 (m, 2C), 127.6, 126.3, 123.1, (q, *J* = 270 Hz, 4C), 122.1 (m, 2C), 120.1, 118.4, 103.8, 83.2, 70.6, 49.1, 29.0, 27.5, 22.5, 1.6 (3C). **HRMS** (ESI+) *m/z* calcd. for $C_{33}H_{30}F_{12}NOSi$ $[M+H]^+$: 712.1900; found: 712.1901.

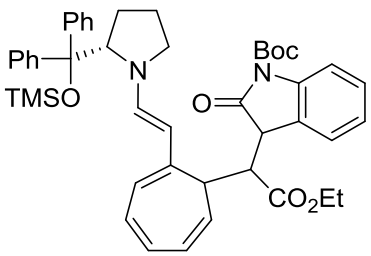
IV.2.4.2 - Intermediates 78a and 78b

In a NMR tube aldehyde **75** (0.10 mmol) and catalyst **IIIa** or catalyst **IIIb** (0.10 mmol, 1.0 equiv.) were dissolved in 0.4 mL of $CDCl_3$ and molecular sieves (4 Å) were added. The reaction mixture was shaken for 15 min and oxindole **42a** (0.10 mmol, 1.0 equiv.) was added. After 1 h the reaction mixture was analyzed by NMR spectroscopy. When catalyst **IIIb** was used the product could be purified by FC (pentane:EtOAc 10:1) affording the pure compound **78b**.



78a

78a: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (m, 1H), 7.93 (m, 1H), 7.86 (m, 3H), 7.77 (m, 4H), 7.31 (m, 2H), 7.18 (d, *J* = 7.5 Hz, 1H), 6.57 (dd, *J* = 10.9, 7.1 Hz, 1H), 6.38 (dd, *J* = 10.9, 6.2 Hz, 1H), 6.26 (dd, *J* = 9.8, 6.2 Hz, 1H), 6.00 (d, *J* = 7.0 Hz, 1H), 5.43 (dd, *J* = 9.2, 9.2 Hz, 1H), 4.95 (d, *J* = 10.5 Hz, 1H), 4.26 (m, 1H), 4.10 (m, 3H), 3.60 (s, 1H), 3.27 (d, *J* = 11.0 Hz, 1H), 2.77 (m, 1H), 2.39 (t, *J* = 9.0 Hz, 1H), 2.12 (m, 1H), 1.7 (m, 1H), 1.64 (s, 9H), 1.13 (t, *J* = 6.8 Hz, 3H), 0.36 (m, 1H), 0.10 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.2, 172.3 149.5, 144.4 (2C), 143.8, 142.0, 141.0, 132.9, 131.7 (q, *J* = 33 Hz, 2C), 131.2 (q, *J* = 34 Hz, 2C), 130.3, 129.3 (m, 2C), 129.2 (m, 2C), 127.7, 127.0, 125.8, 125.0, 124.1, 123.6, 123.5, 123.0 (q, *J* = 273 Hz, 4C), 122.2 (m, 1C), 122.0 (m, 1C), 114.6, 103.8, 83.6, 83.0, 70.6, 60.5, 48.7, 45.5, 41.4, 36.4, 28.1 (3C), 27.2, 22.5, 13.9, 1.6 (3C). **HRMS** (ESI+) *m/z* calcd. for $C_{50}H_{51}F_{12}N_2O_6Si$ $[M+H]^+$: 1031.3319; found: 1031.3330.

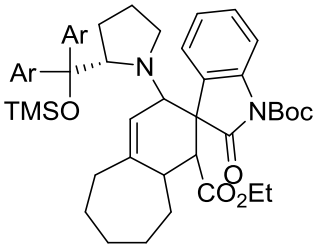


78b

78b: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.22 (m, 14H), 6.53 (dd, *J* = 10.7, 7.2 Hz, 1H), 6.28 (dd, *J* = 10.7, 6.2 Hz, 1H), 6.20 (dd, *J* = 8.9, 6.2 Hz, 1H), 5.90 (d, *J* = 7.2 Hz, 1H), 5.24 (dd, *J* = 8.9, 8.9 Hz, 1H), 4.71 (d, *J* = 13.5 Hz, 1H), 4.28 (m, 1H), 4.16 (m, 1H), 4.05 (m, 1H), 3.91 (m, 1H), 3.58 (s, 1H), 3.21 (d, *J* = 11.3 Hz, 1H), 2.68 (m, 1H), 2.41 (t, *J* = 9.1 Hz, 1H), 1.94 (m, 2H), 1.66 (s, 9H), 1.38 (m, 1H), 1.16 (t, *J* = 7.0 Hz, 3H), 0.28 (m, 1H), 0.14 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.3, 172.3 149.5, 142.3 (2C), 141.8, 141.6, 141.0, 132.6, 130.5, 129.9 (2C), 129.2 (2C), 127.8, 127.6, 127.5 (2C), 127.3 (2C), 127.3, 126.8, 126.3, 124.3, 123.6, 123.4, 117.7, 114.6, 100.4, 83.5, 83.2, 69.9, 60.4, 48.2, 45.7, 41.4, 36.4, 28.2

(3C), 27.3, 22.3, 14.0, 1.9 (3C). **HRMS** (ESI+) *m/z* calcd. for $C_{46}H_{55}N_2O_6Si$ $[M+H]^+$: 759.3824; found: 759.3834.

IV.2.4.3 - Product 83



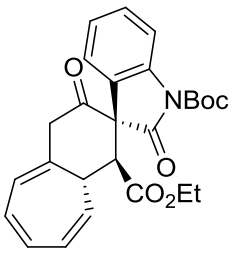
83

In a glass vial a mixture of oxindole **42a** (0.10 mmol, 1.0 equiv.), *o*-FBA (0.02 mmol, 0.2 equiv.) catalyst **IIIa** (0.02 mmol, 0.2 equiv.) were dissolved in 0.4 mL of $CHCl_3$ and aldehyde **5** (0.12 mmol, 1.2 equiv.) was added. The mixture was stirred at rt or 40 °C for 48 h and monitored by ^{1}H NMR spectroscopy. Compound **83** was the only product detected. For the full characterization of **83** the reaction was performed with 1.0 equiv. of **IIIa**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.94 (s, 2H), 7.90 (s, 1H), 7.80 (s, 2H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.33 (m, 1H), 7.17 (dt, *J* = 14.8, 7.3 Hz, 2H), 5.73 (s, 1H), 4.12 (d, *J* = 9.3 Hz, 2H), 3.93 (m, 2H), 3.49 (dd, *J* = 17.2, 7.3 Hz, 1H), 3.38 (d, *J* = 10.7 Hz, 1H), 3.13 (d, *J* = 9.8 Hz, 1H), 2.51 (m, 4H), 2.01 (m, 1H), 1.92 (dd, *J* = 13.7, 5.0 Hz, 1H), 1.79 (s, 9H), 1.64 (m, 3H), 1.51 (m, 6H), 1.05 (t, *J* = 7.1 Hz, 3H), 0.50 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.1, 171.5, 149.1, 145.7, 145.0, 144.4, 137.8, 131.3 (q, *J* = 32.9 Hz, 2C), 130.6, 130.2 (q, *J* = 32.9 Hz, 2C), 130.2 (m, 2C), 128.9 (m, 2C), 128.1, 124.4, 123.8, 123.3 (q, *J* = 271.59 Hz, 2C), 123.0 (q, *J* = 271.59 Hz, 2C) 122.1 (m, 1C), 121.7, 121.2 (m, 1C), 114.0, 85.1, 84.5, 69.1, 62.6, 60.7, 54.4, 49.9, 48.2, 37.2, 35.6, 31.9, 30.7, 29.5, 29.2, 28.1 (3C), 25.3, 22.6, 13.5, 1.0 (3C). **HRMS** (ESI+) *m/z* calcd. for $C_{50}H_{55}F_{12}N_2O_6Si$ $[M+H^+]^+$: 1035.3632; found: 1035.3635.

IV.2.5 - Transformations

IV.2.5.1 - Product 84

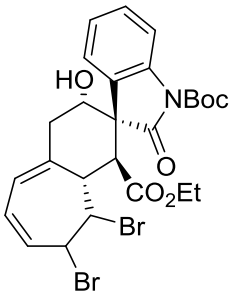


84

In a glass vial cycloadduct **77a** (45.1 mg, 0.1 mmol, 1.0 equiv.) was solved in $CHCl_3$ (1 mL) and cooled to −20 °C. A solution of Dess Martin periodinane (72.0 mg, 0.17 mmol, 1.7 equiv.) in $CHCl_3$ (1 mL) was added to the solution and the reaction mixture was warmed to rt. After 1 h an additional 0.5 equiv. of Dess Martin periodinane was added and the reaction mixture was stirred for further 30 min. The reaction mixture was plugged over Iatrobeads, the solvent was removed in vacuum and the product was purified by FC (pentane:EtOAc 15:1) to afford the pure compound **84** in 94% yield and >95:5 dr.

Colourless oil. $[\alpha]_D^{20}$ = −222.4 (*c* 0.53, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.2 Hz, 1H), 7.30 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.02 (dd, *J* = 7.6, 7.8 Hz, 1H), 6.80 (m, 2H), 6.69 (dd, *J* = 11.0, 5.6 Hz, 1H), 6.30 (dd, *J* = 9.2, 5.6 Hz, 1H), 6.21 (d, *J* = 5.6 Hz, 1H), 5.29 (dd, *J* = 9.2, 4.7 Hz, 1H), 4.25 (d, *J* = 12.5 Hz, 1H), 3.87 (m, 2H), 3.79 (d, *J* = 16.8 Hz, 1H), 3.36 (d, *J* = 16.8 Hz, 1H), 2.60 (dd, *J* = 12.5, 4.7 Hz, 1H), 1.65 (s, 9H), 0.93 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.8, 172.9, 169.21, 148.7, 141.3, 131.8, 129.5, 129.4, 126.0, 125.4, 124.7, 124.6, 124.5, 123.7, 123.2, 115.5, 84.7, 64.5, 61.4, 49.7, 46.9, 37.9, 28.0 (3C), 13.4. **HRMS** (ESI+) *m/z* calcd. for $C_{26}H_{27}NO_6Na$ $[M+Na]^+$: 472.1731; found: 472.1731.

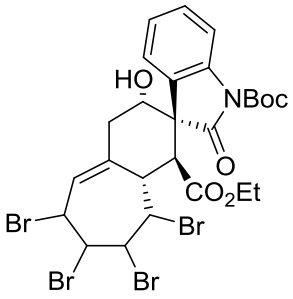
IV.2.5.2 - Product 85



85

In a dry flask under Ar cycloadduct **77a** (45 mg, 0.1 mmol, 1.0 equiv.) was dissolved in dry $CDCl_3$ (2 mL) and cooled to −78 °C. A freshly prepared solution of Br_2 (1.0 M in $CDCl_3$, 100 µL, 0.1 mmol, 1.0 equiv.) was added dropwise. The mixture was kept at −78 °C for 2 h. The crude NMR indicates a full conversion of **77a** and a clean formation of **85**, which is stable in solution.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.1 Hz, 1H), 7.35 (m, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.05 (d, *J* = 7.7 Hz, 1H), 5.94 (dd, *J* = 11.6, 7.7 Hz, 1H), 5.87 (dd, *J* = 11.6, 5.9 Hz, 1H), 5.17 (m, 1H), 4.68 (d, *J* = 4.3 Hz, 1H), 4.28 (br d, *J* = 11.3 Hz, 1H), 3.99 (d, *J* = 11.3 Hz, 1H), 3.87 (dd, *J* = 6.4, 2.9 Hz, 1H), 3.74 (m, 2H), 2.86 (m, 2H), 1.66 (s, 9H), 0.85 (t, *J* = 7.1 Hz, 3H).

IV.2.5.3 - Product 86



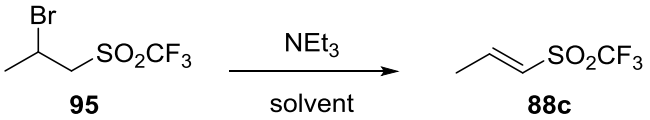
86

In a dry flask under Ar cycloadduct **77a** (45 mg, 0.1 mmol, 1.0 equiv.) was dissolved in dry $CDCl_3$ (2 mL) and cooled to −78 °C. A freshly prepared solution of Br_2 (1.0 M in $CDCl_3$, 100 µL, 0.1 mmol, 1.0 equiv.) was added dropwise. The mixture was kept at −78 °C for 1 h and again a solution of Br_2 (1.0 M in $CDCl_3$, 200 µL, 0.2 mmol, 2.0 equiv.) was added. After additional 6 h ^{1}H NMR analysis of the crude indicated full conversion of starting material. The reaction was quenched with sat. $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (3 x 10 mL) giving the clean product **86** in 71 % yield.
Yellow foam. $[\alpha]_D^{20}$ = +66.4 (*c* 0.33, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.35 (m, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 6.26 (d, *J* = 3.0 Hz, 1H), 5.46 (m, 1H), 5.17 (dd, *J* = 5.7, 3.3 Hz, 1H), 4.96 (dd, *J* = 7.9, 5.7 Hz, 1H), 4.72 (dd, *J* = 3.3, 1.3 Hz, 1H), 4.29 (br d, *J* = 11.2 Hz, 1H), 3.93 (d, *J* = 11.2 Hz, 1H), 3.84 (m, 1H), 3.74 (m, 2H), 3.13 (br s, 1H), 2.87 (dd, *J* = 14.1, 8.5 Hz, 1H), 2.70 (d, *J* = 14.1 Hz, 1H), 1.66 (s, 9H), 0.86 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.5, 169.8, 148.9, 140.0, 138.7, 129.4, 127.7, 127.7, 125.0, 124.5, 115.2, 85.0, 72.4, 61.6, 55.6, 55.6, 55.4, 55.2, 49.1, 48.4, 39.7, 36.7, 28.1 (3C), 13.3. **HRMS** (ESI+) *m*/*z* calcd. for $C_{26}H_{30}Br_4NO_6$ $[M+H]^+$: 767.8801; found: 767.8801.

IV.3 - Experimental Procedures for the enamine-mediated Michael addition reactions

Catalyst **XI** was prepared according to the procedure described in the literature[25] or was already available from previous projects.

IV.3.1 - Synthesis of (*E*)-1-((trifluoromethyl)sulfonyl)prop-1-ene 88c[55]



95 **88c**

To a solution of 2-bromo-1-((trifluoromethyl)sulfonyl)propane **95** (25 mg, 0.1 mmol, 1.0 equiv.) in solvent (0.4 mL) was added, triethylamine (13.9 µL, 0.1 mmol, 1.0 equiv.) dropwise.
After 30 min ^{1}H NMR showed full conversion of the starting material and the reaction was quenched with 1.0 mL of HCl (1.0 M) and washed with H_2O several times. The solution was dried with 4Å molecular sieves and transferred to another vial affording the title compound in 70% yield. This compound was used for the Michael addition reactions without further purification and the solvent in which the elimination was preformed was the same as the one used in the Michael reaction. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (dq, *J* = 14.0, 7.0 Hz, 1H), 6.38 (ddd, *J* = 15.1, 1.5, 0.7 Hz, 1H), 2.13 (dd, *J* = 7.0, 1.6 Hz, 3H).

IV.3.2 - General procedure for the Michael addition reactions

In a glass vial was mixed aldehyde **5** (1.5 equiv.), the aminocatalyst (0.2 equiv.), additive (0.2 equiv.) and the vinylsulfone **88** (1.0 equiv.) in the appropriate solvent (0.25 M) and the reaction was allowed to raise to the desired temperature.
The reaction was controlled by ^{1}H NMR spectroscopy over 24h (for reactions at 40 or 60 °C) or 48h for reactions carried out at rt.

Chapter V - References

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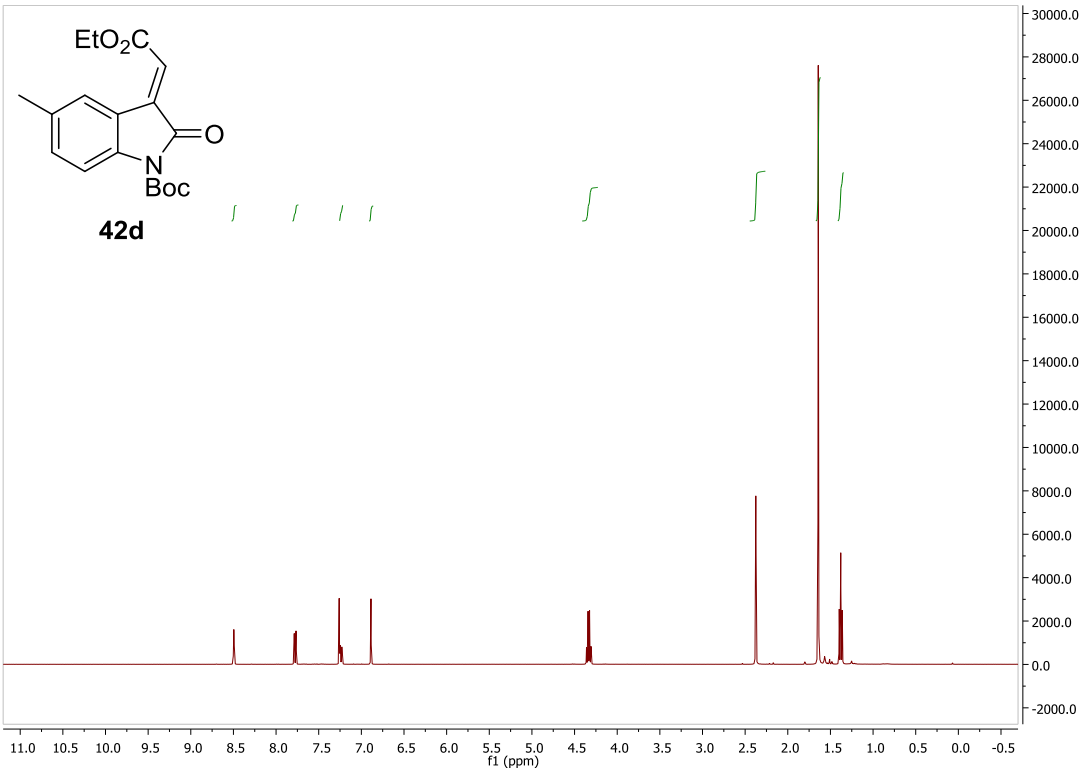
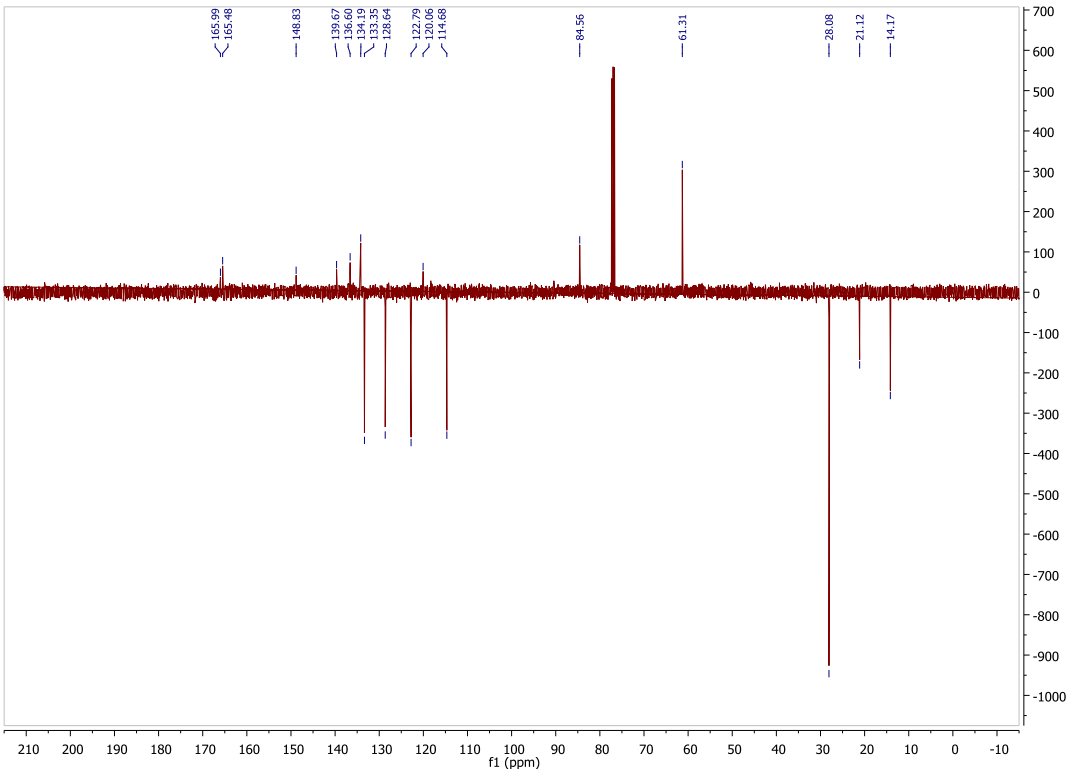
Chapter VI - Annexes



^{1}H NMR spectrum of **42d**



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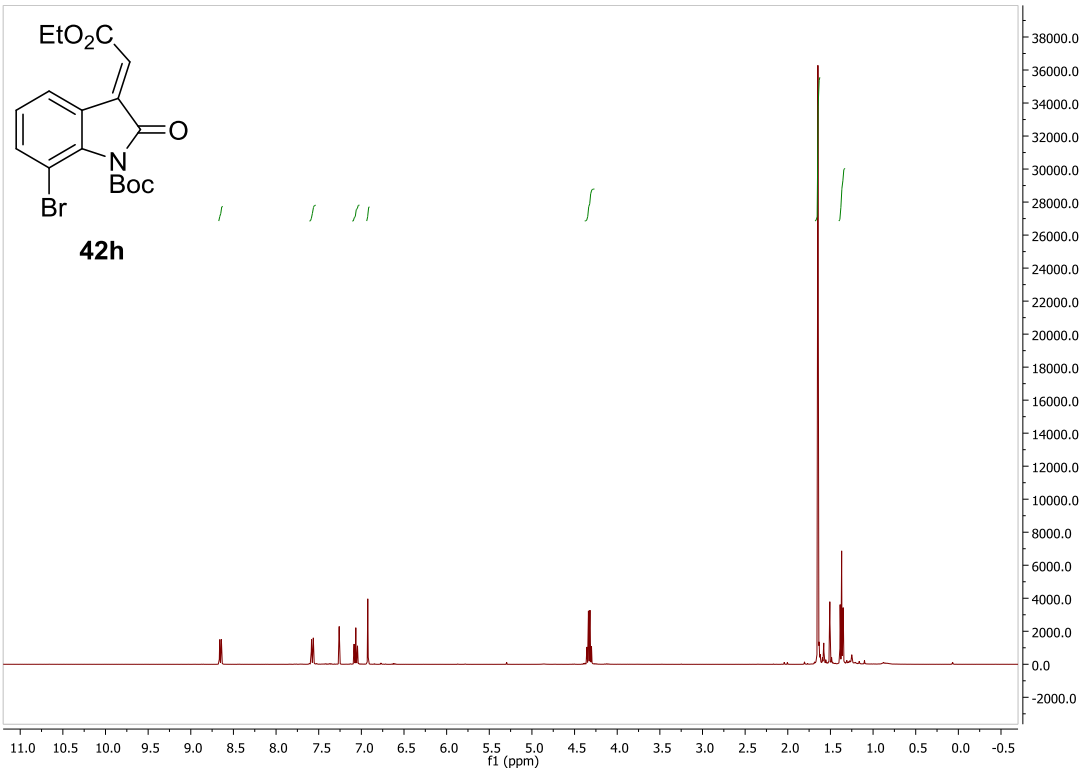

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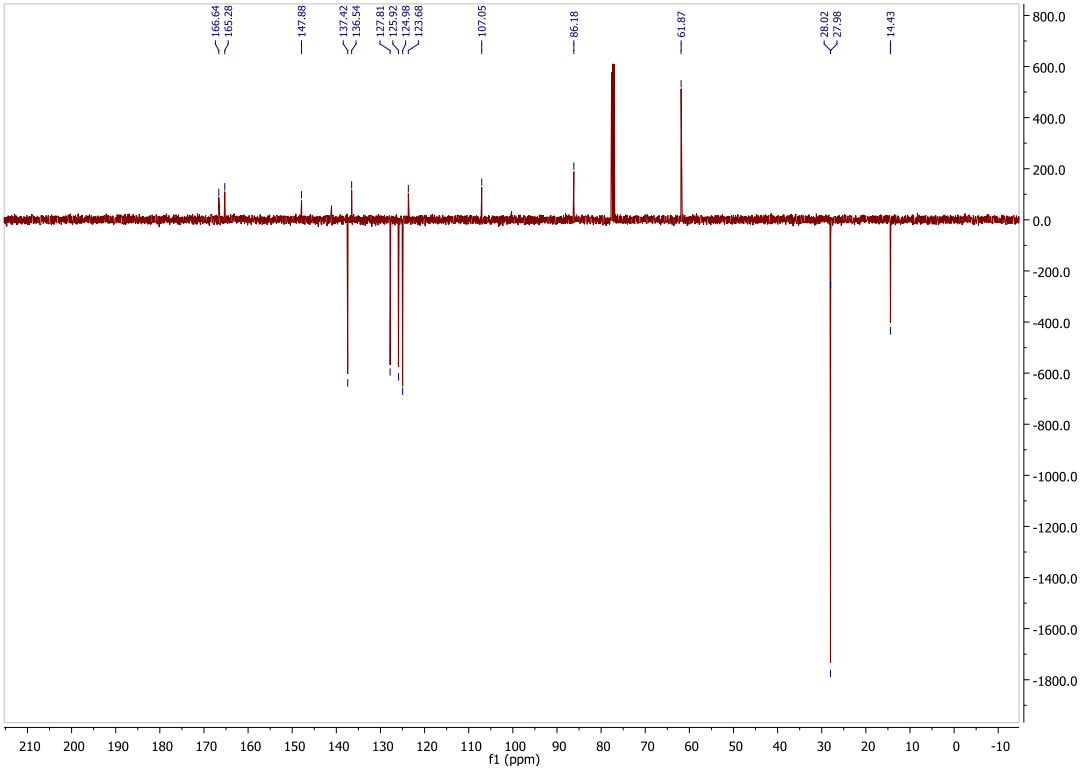

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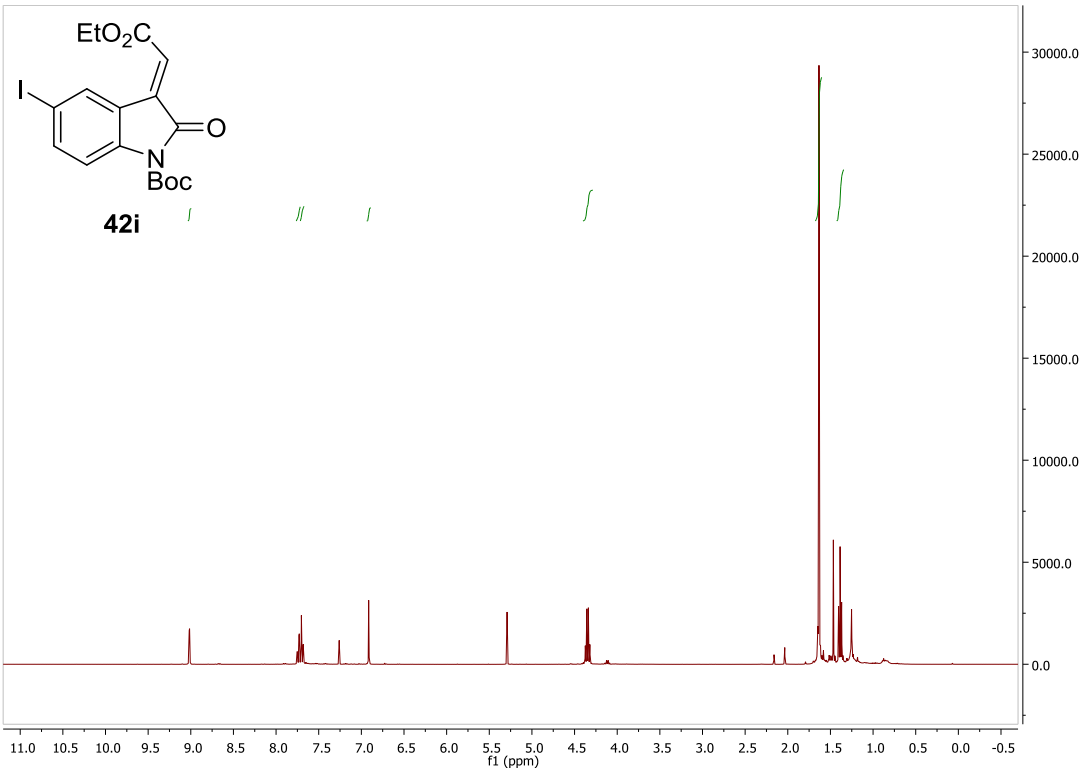

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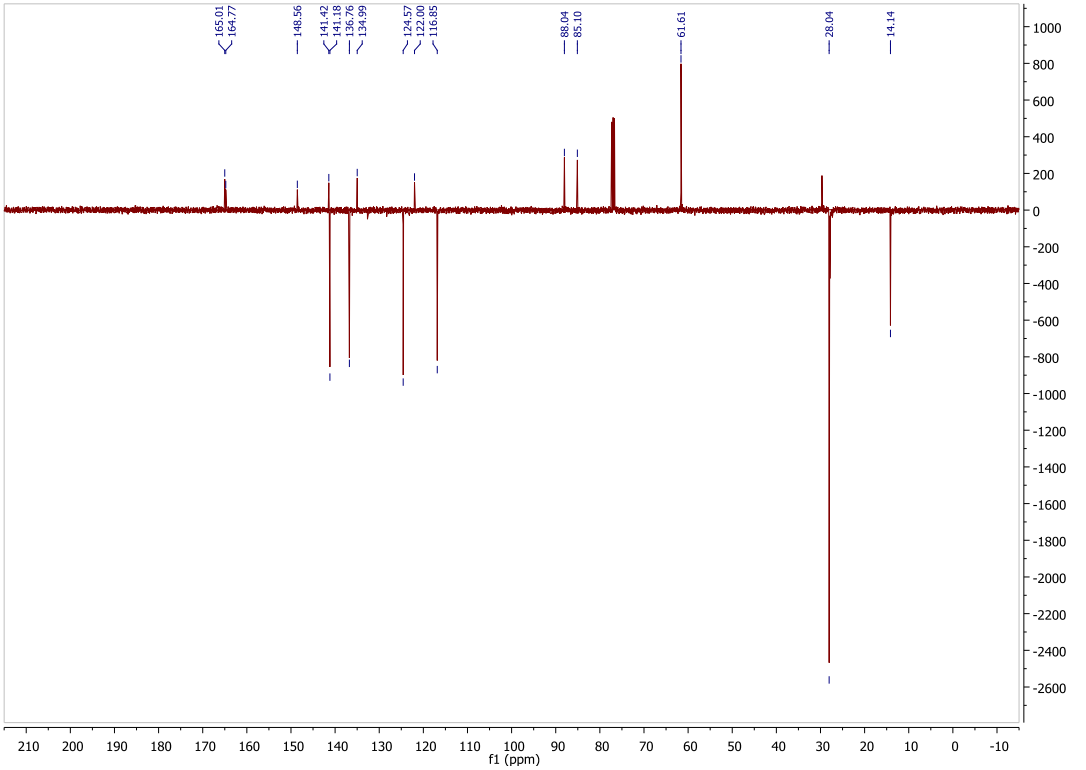

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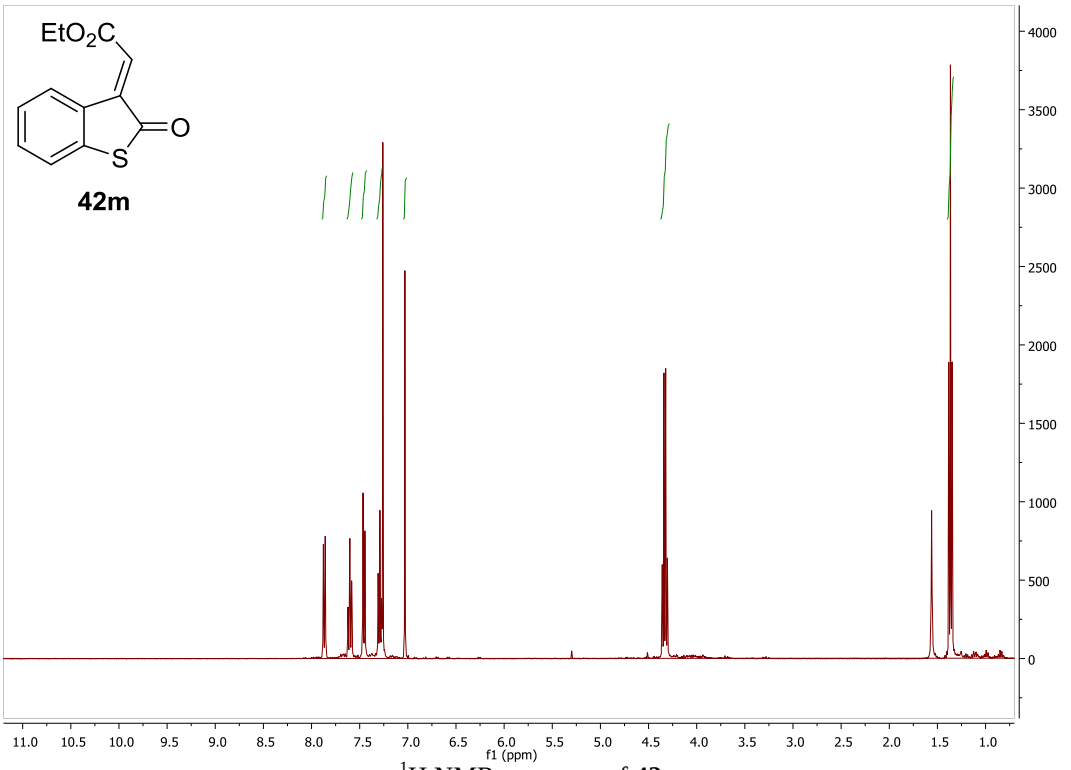

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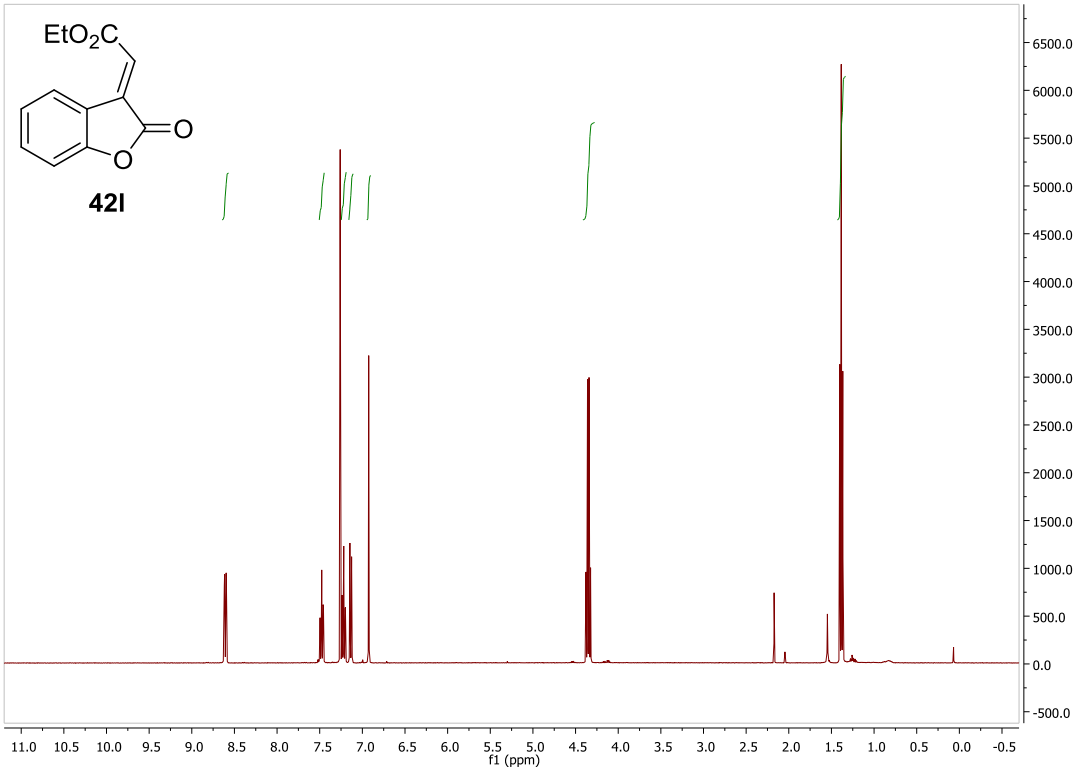

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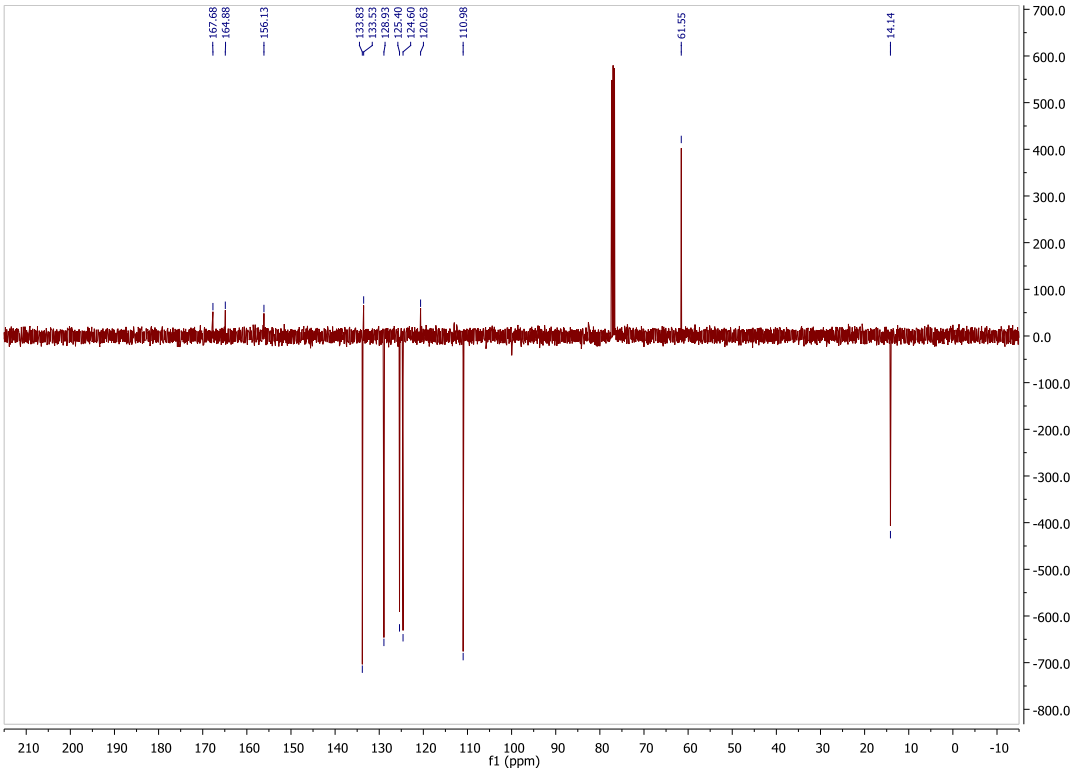

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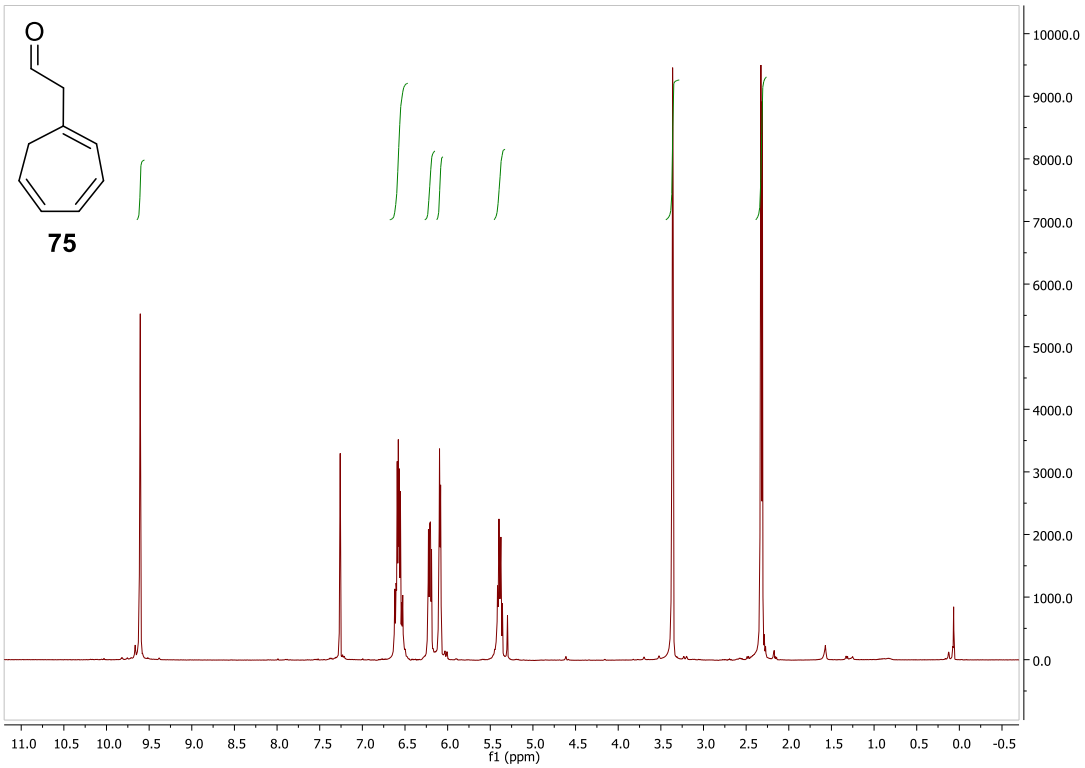

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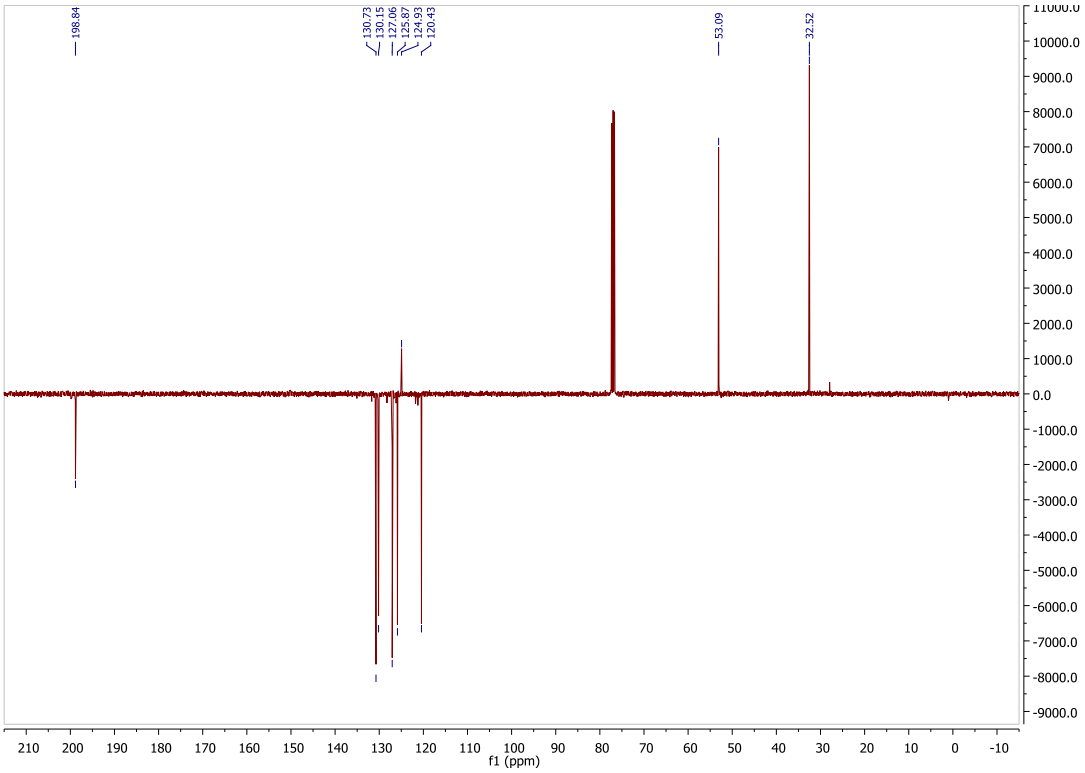

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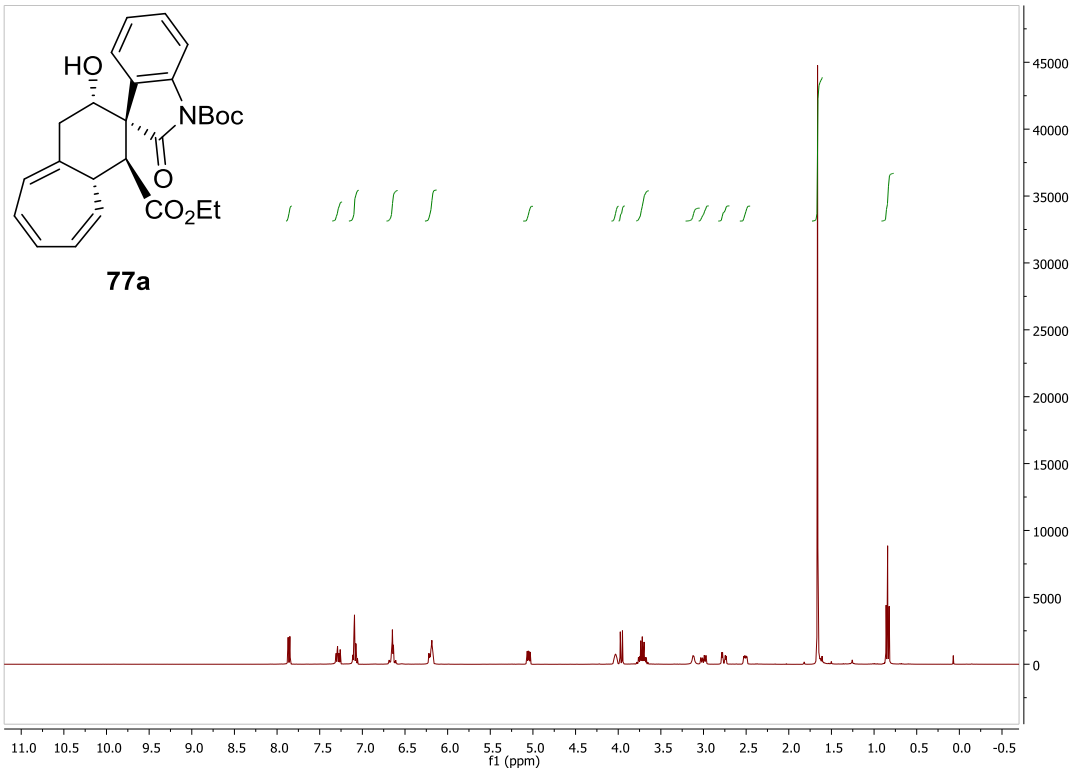

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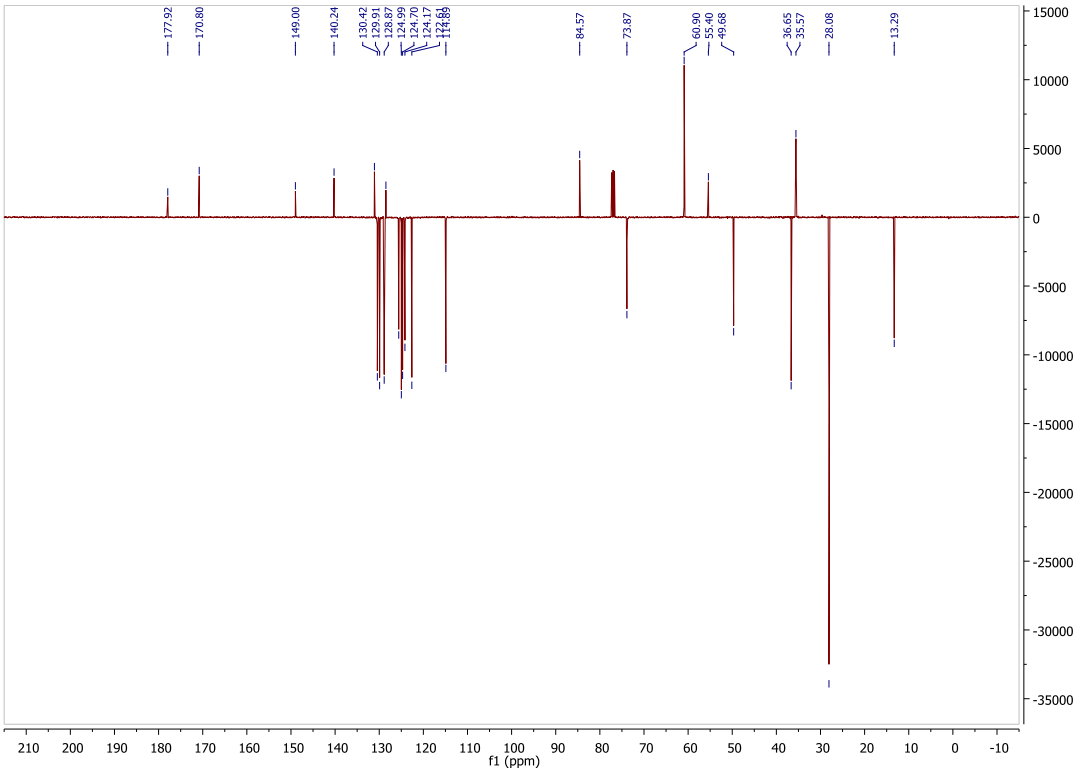

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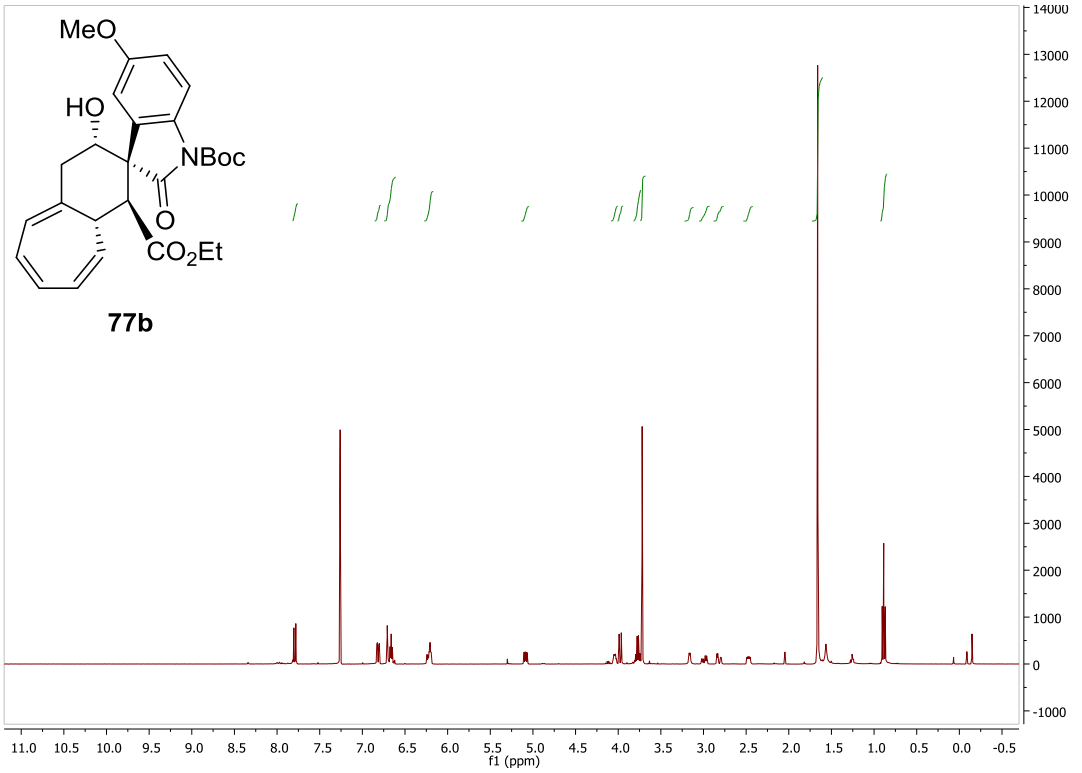

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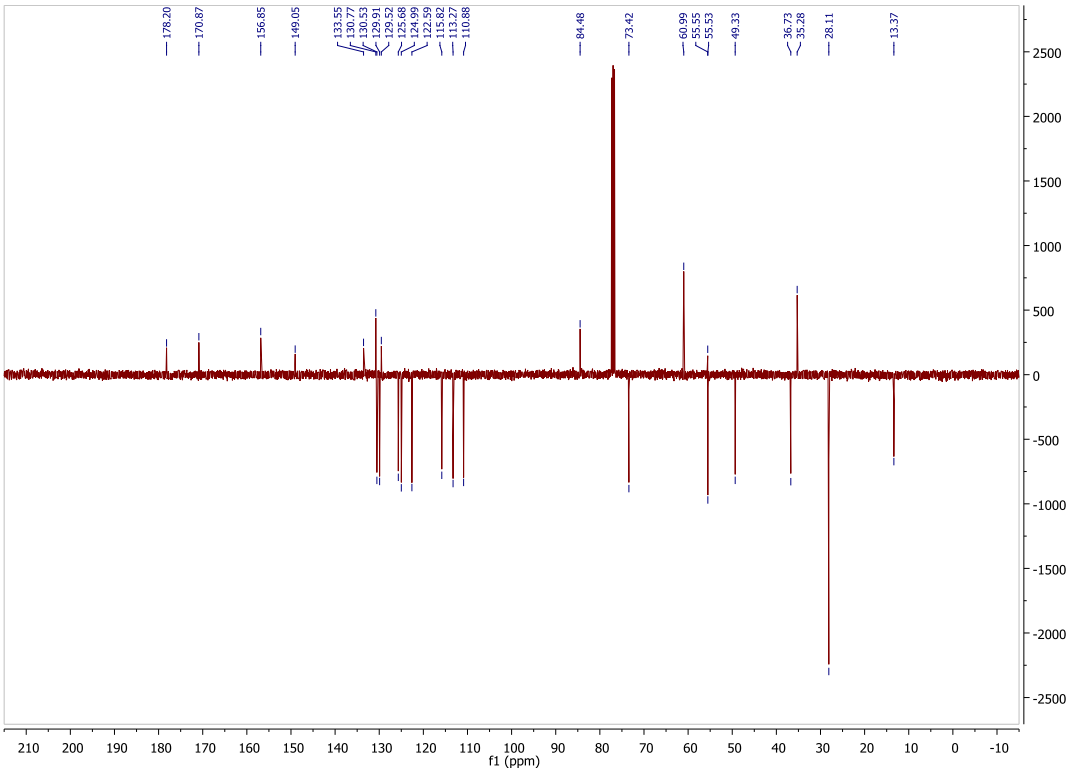

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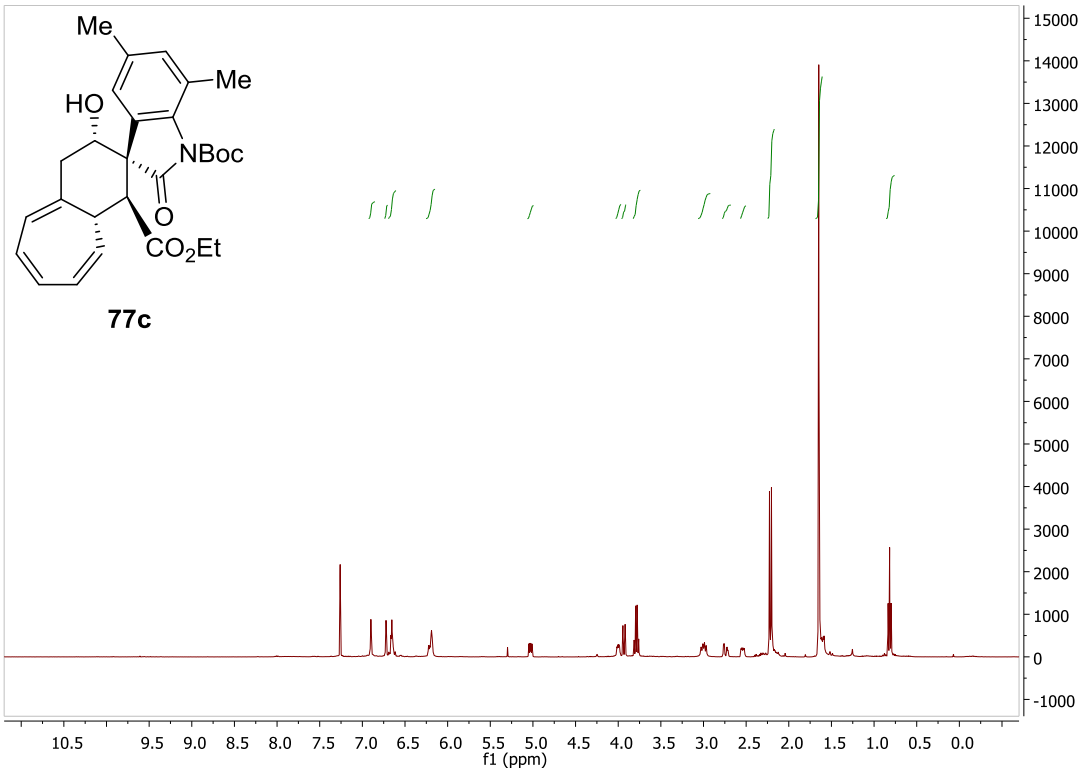

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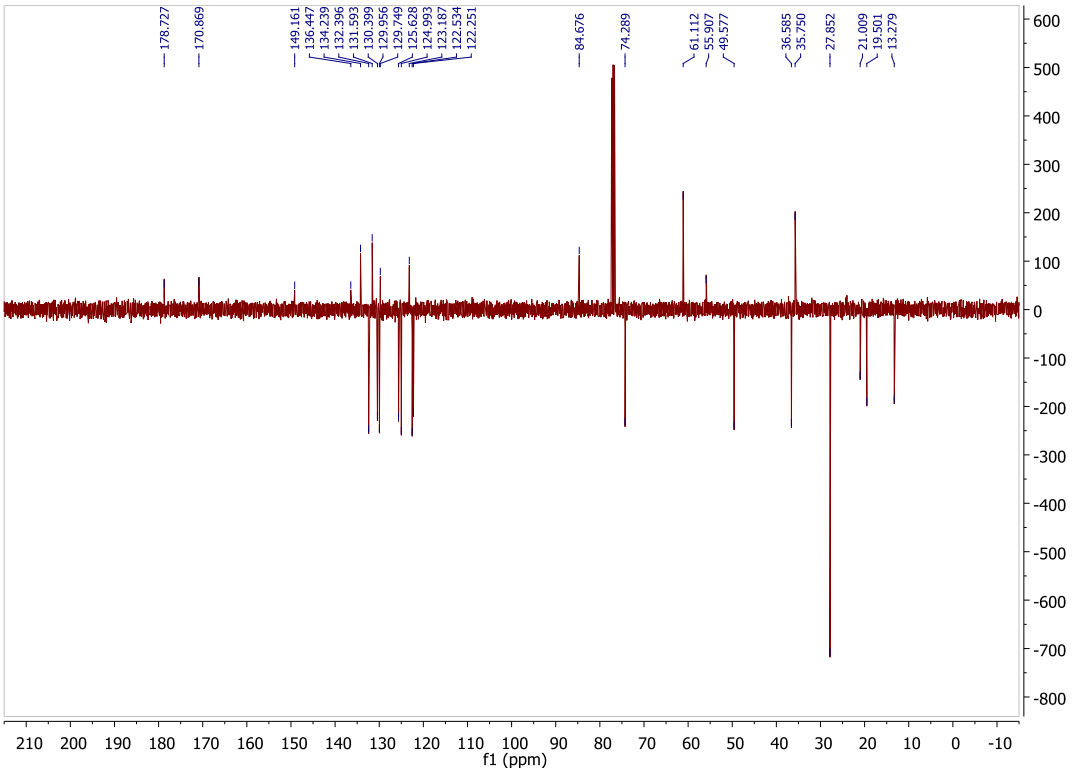

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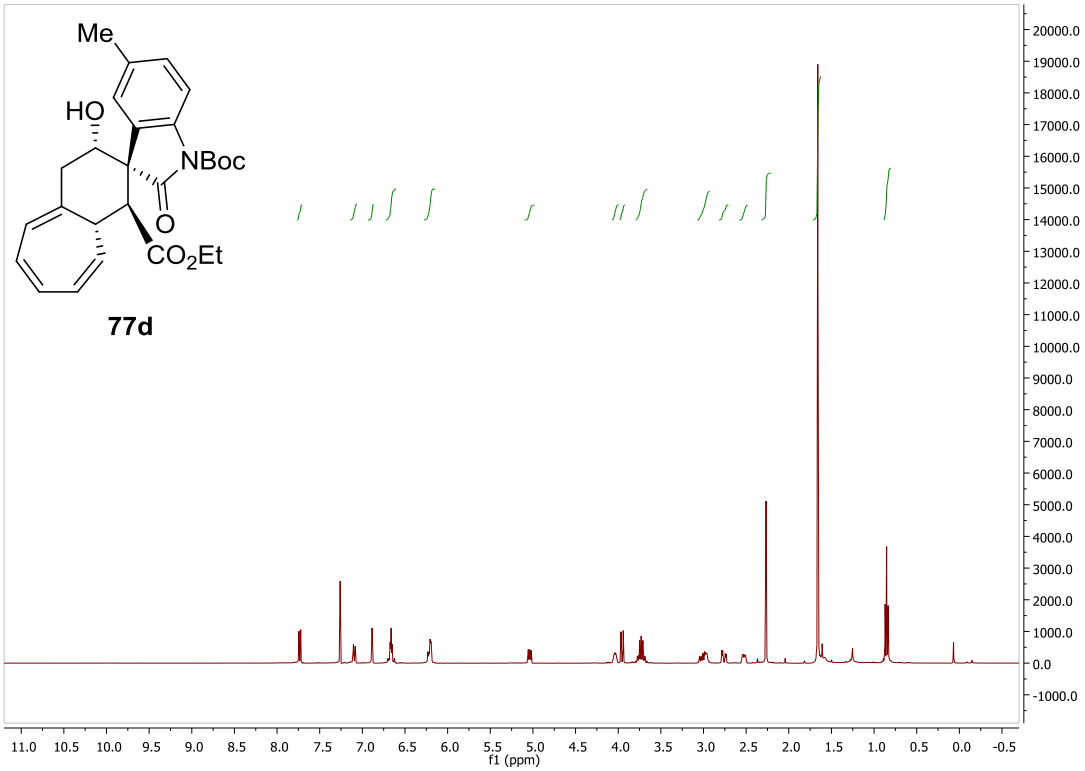

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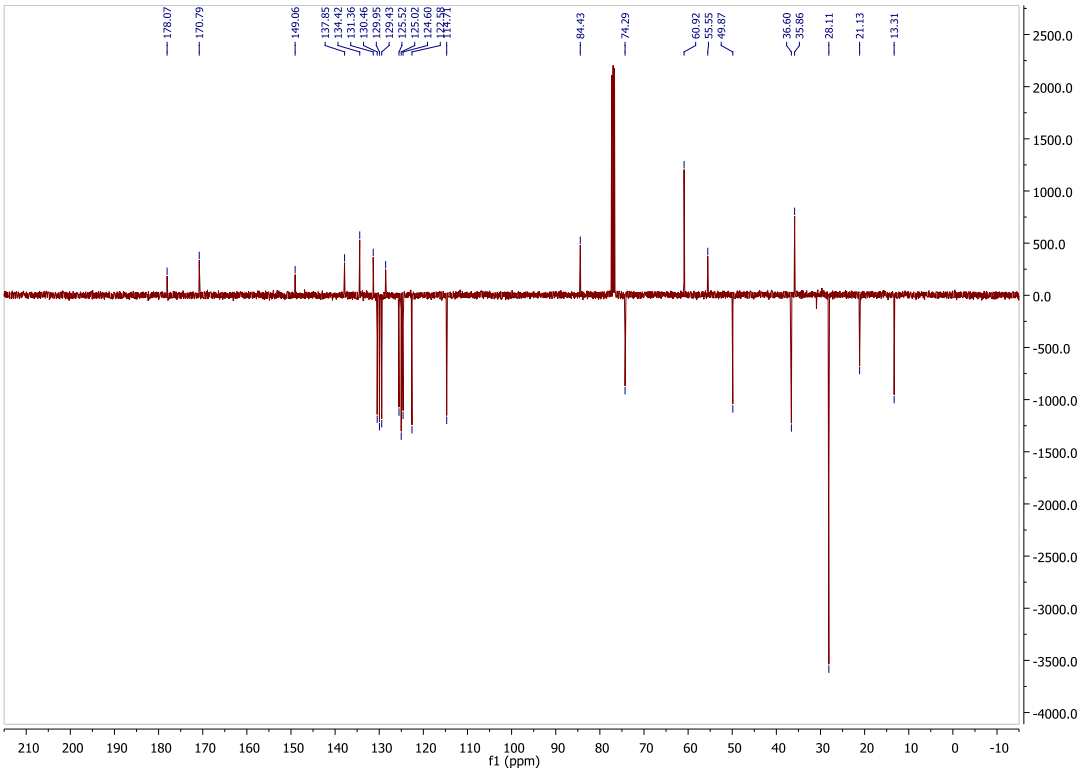

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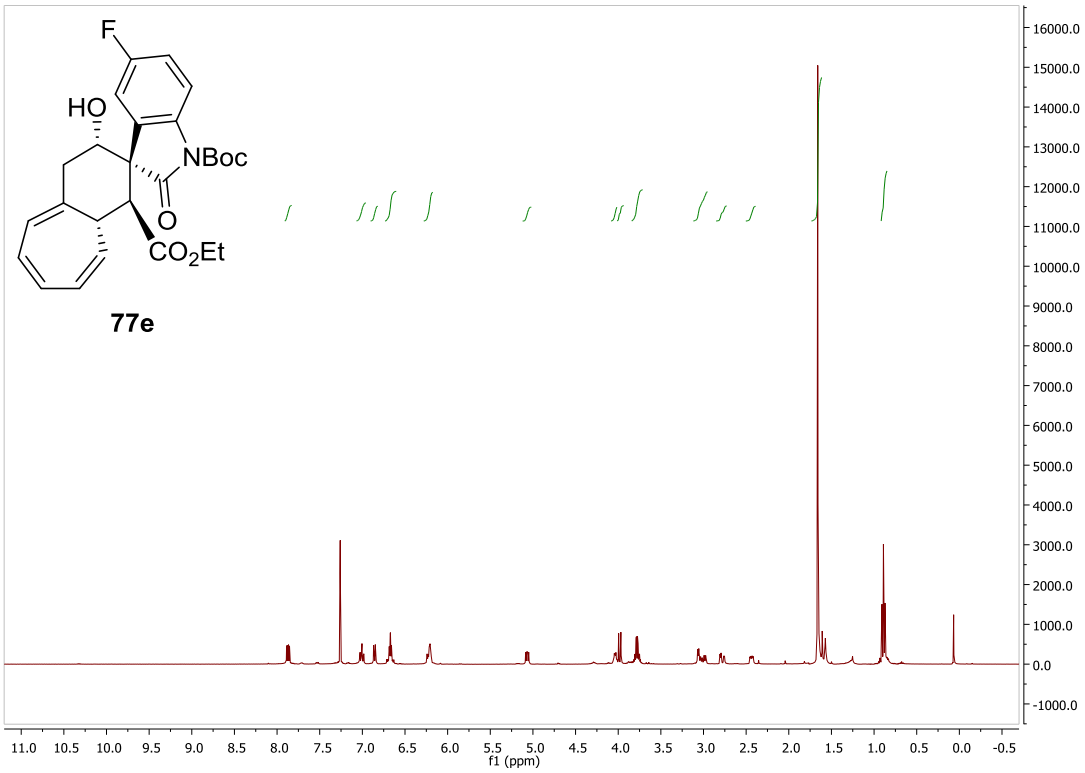
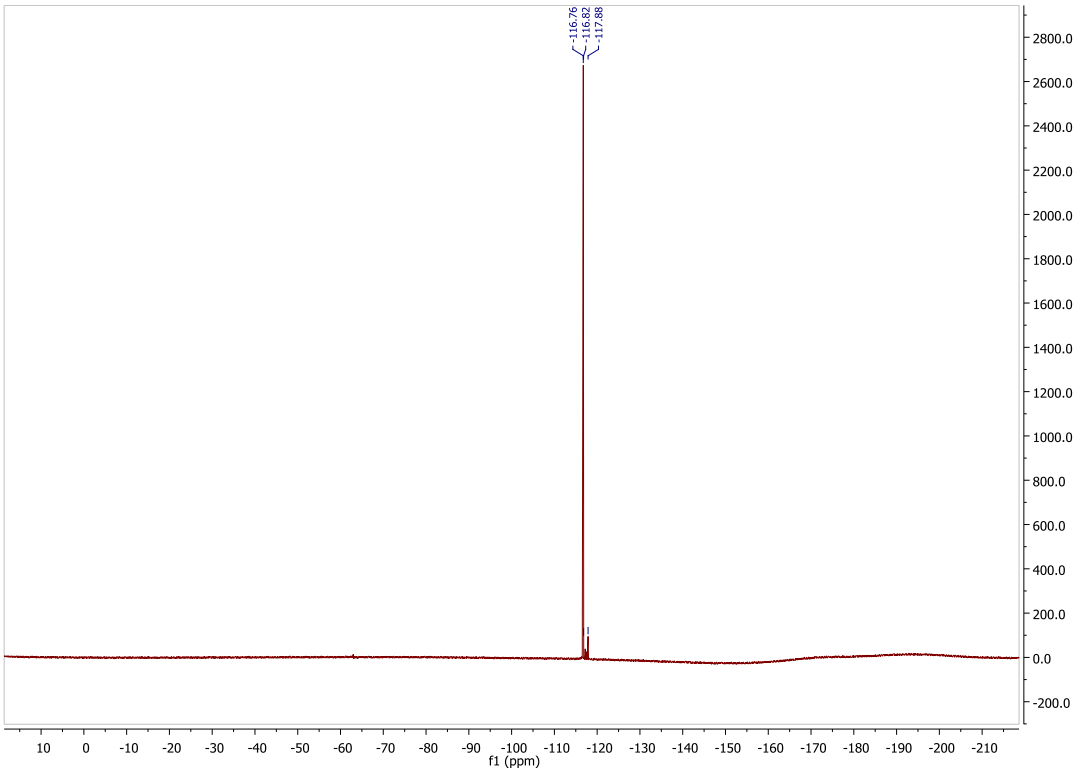
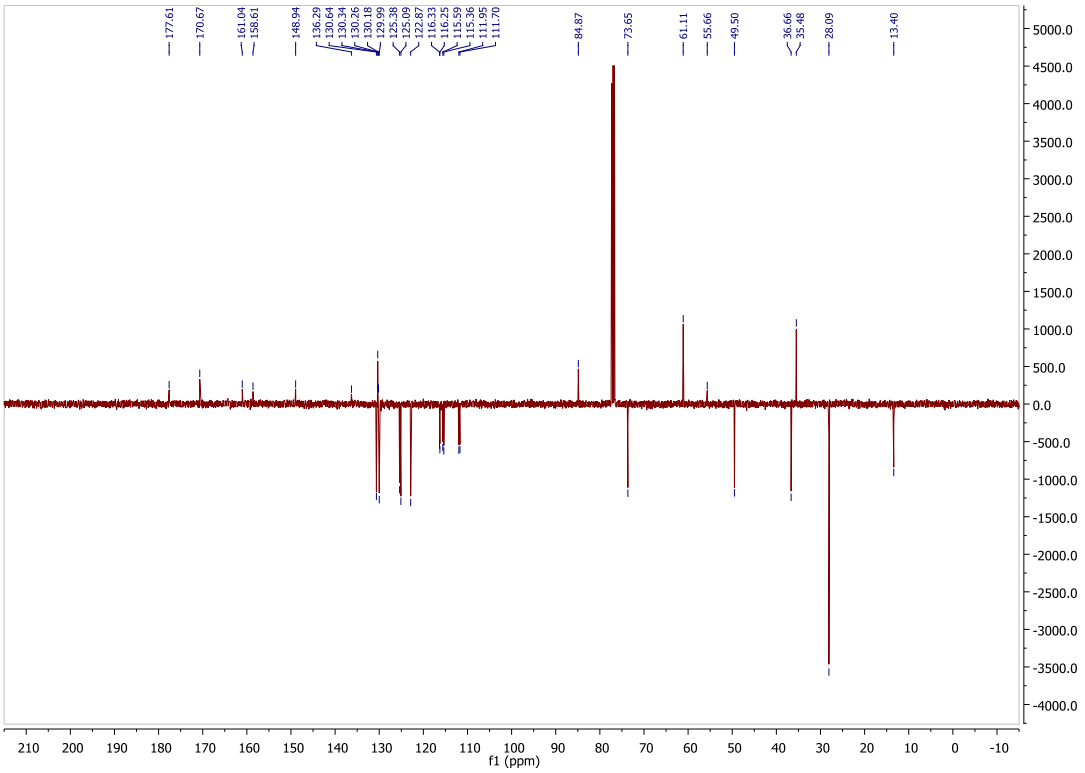


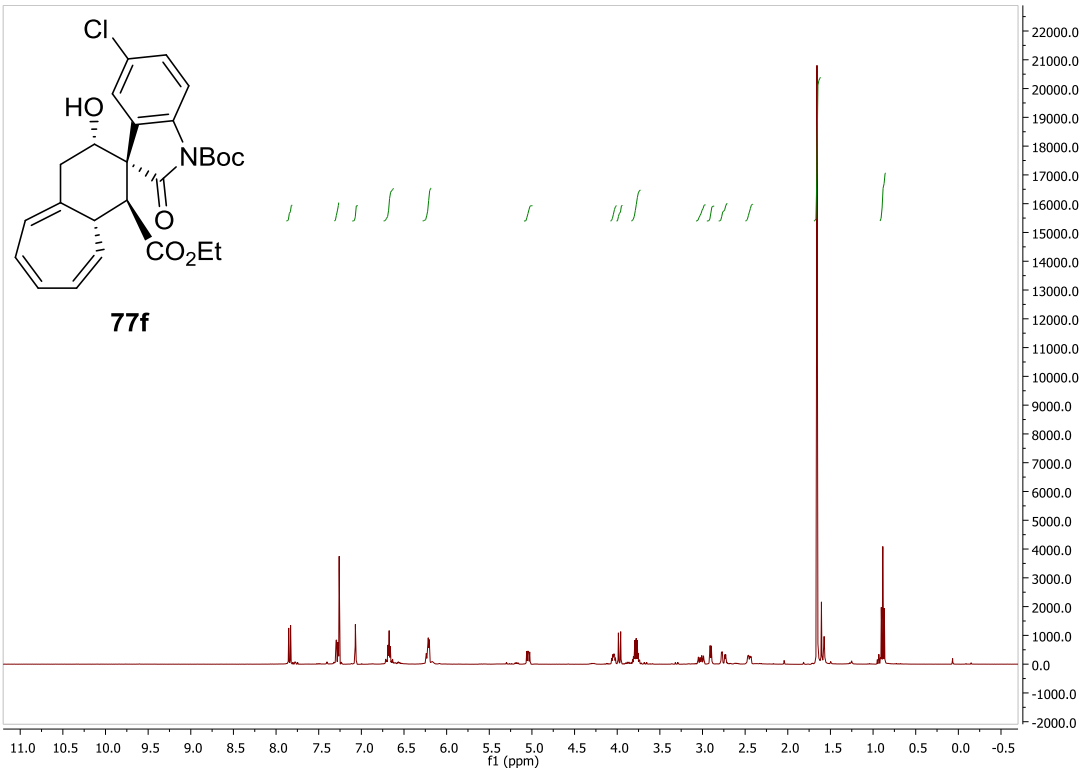
^{1}H NMR spectrum of **77e**



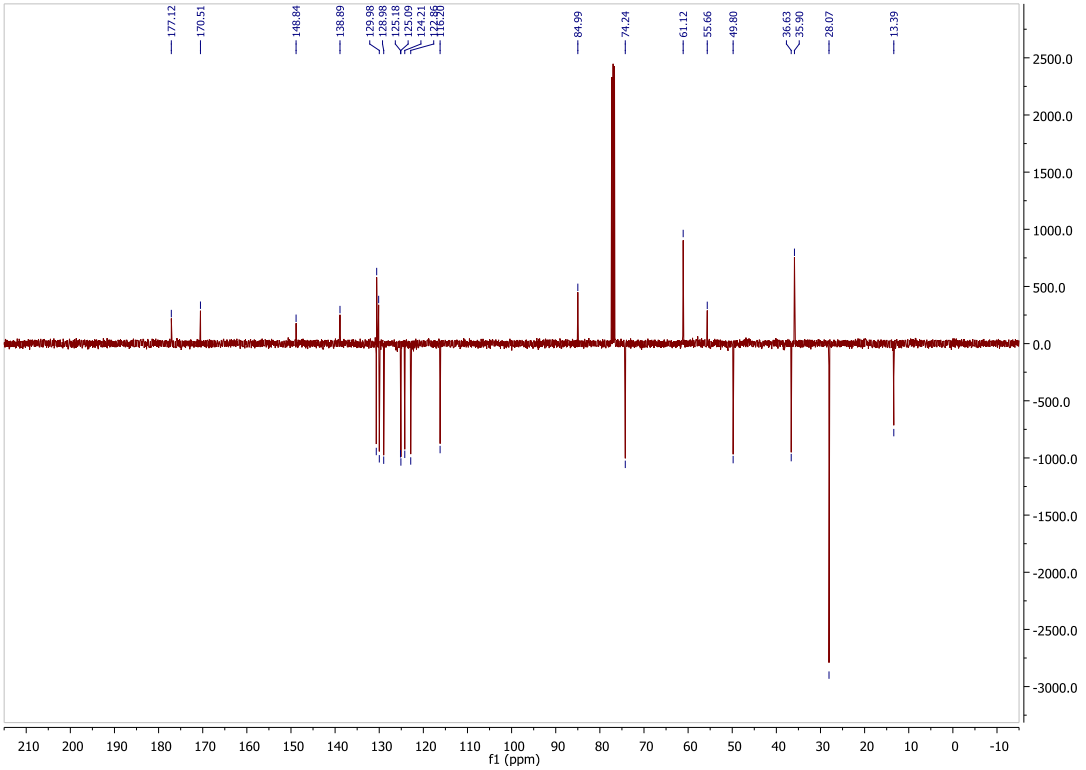
^{19}F NMR spectrum of **77e**



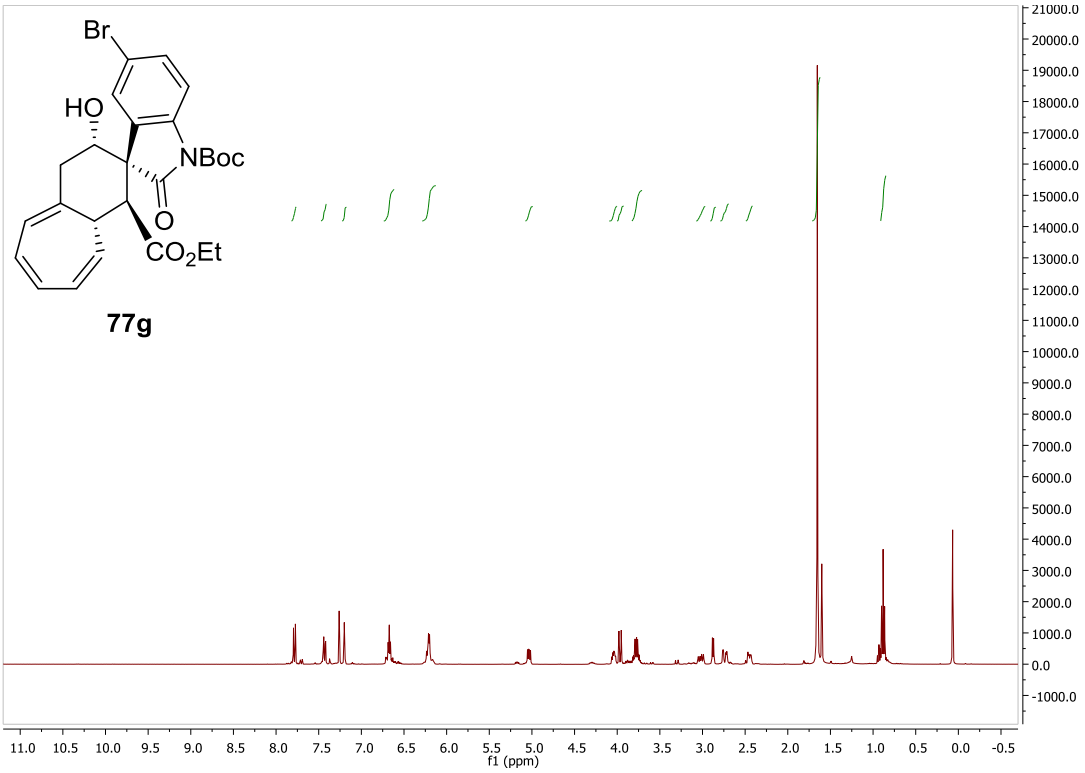
^{13}C NMR spectrum of **77e**



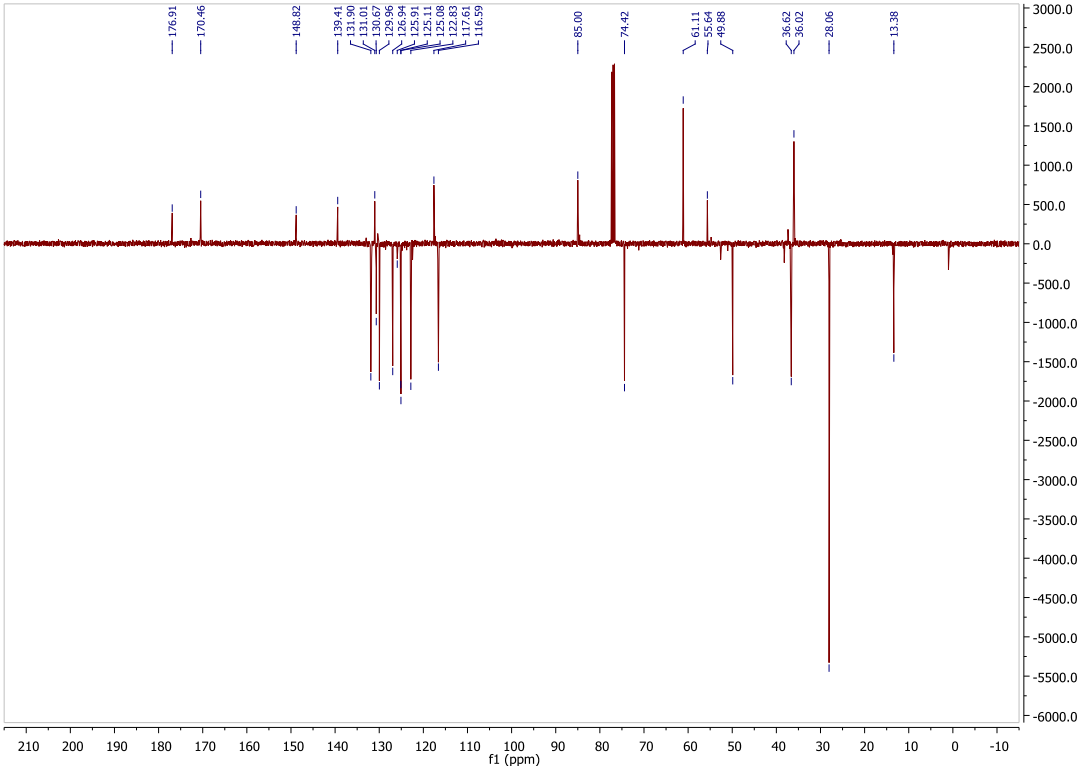
^{1}H NMR spectrum of **77f**



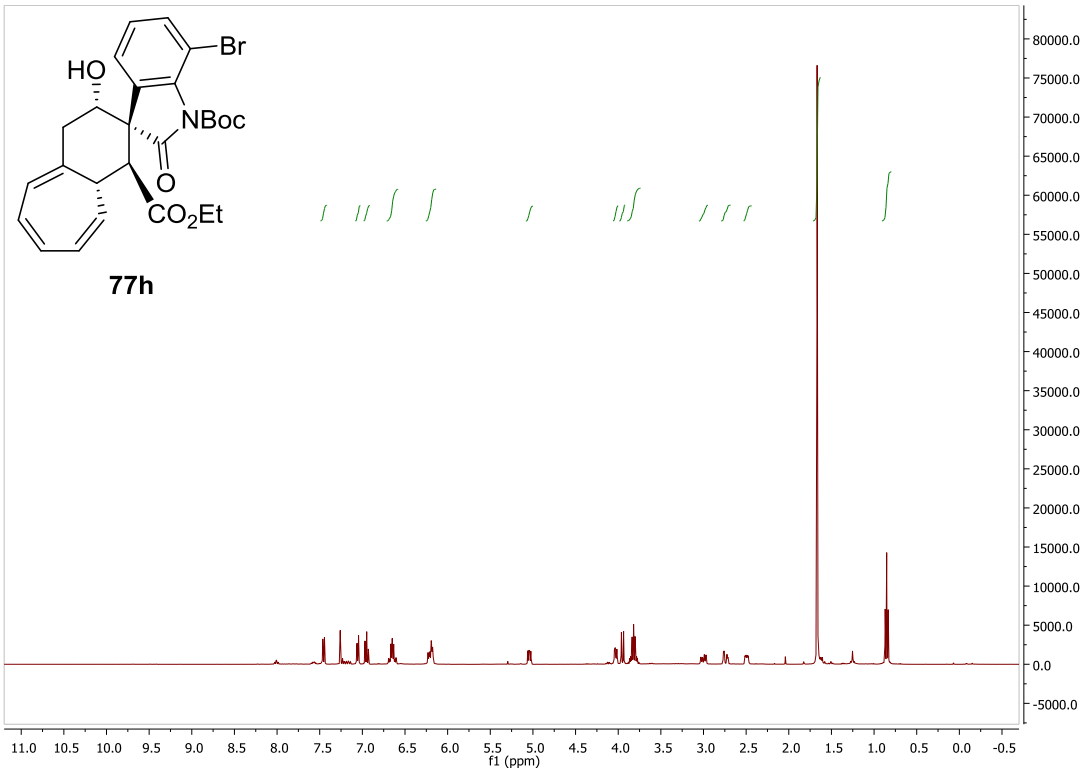
^{13}C NMR spectrum of **77f**



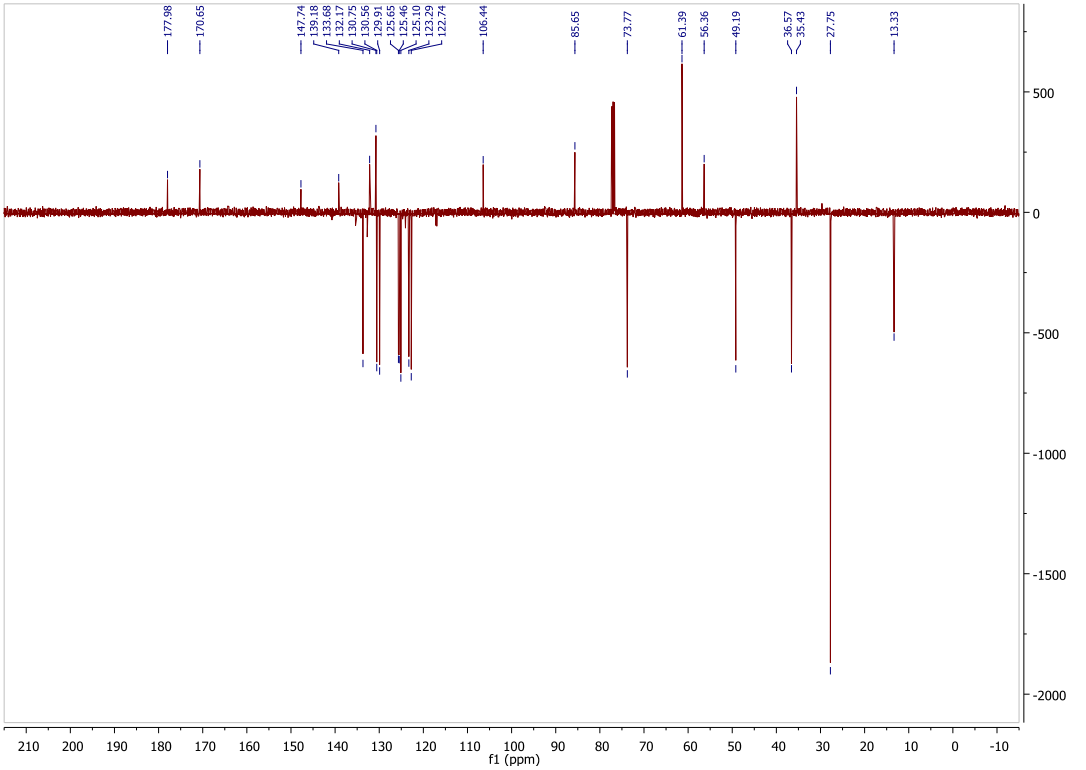
^{1}H NMR spectrum of **77g**



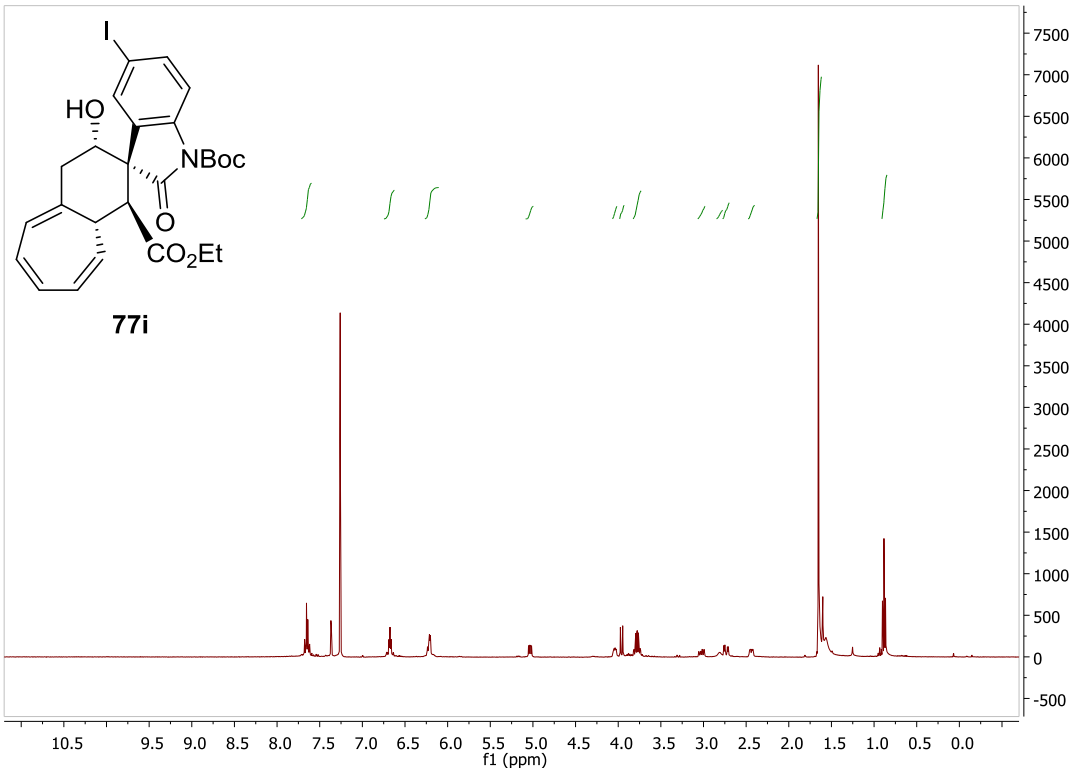
^{13}C NMR spectrum of **77g**



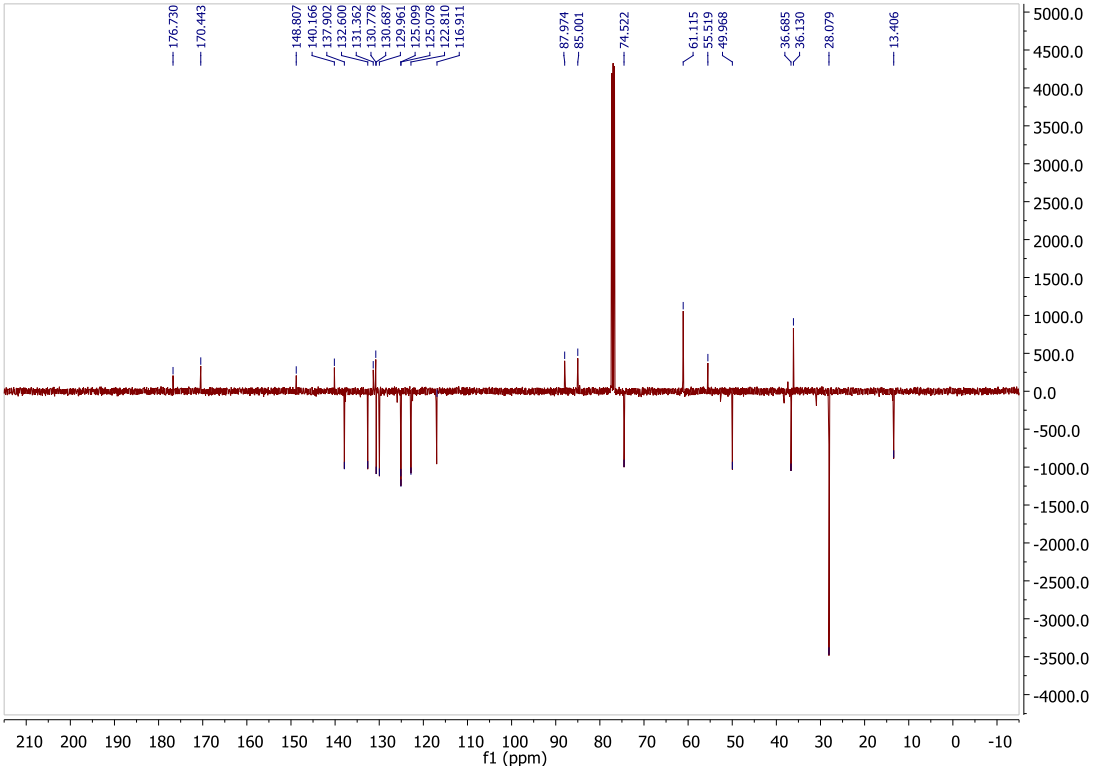
^{1}H NMR spectrum of **77h**



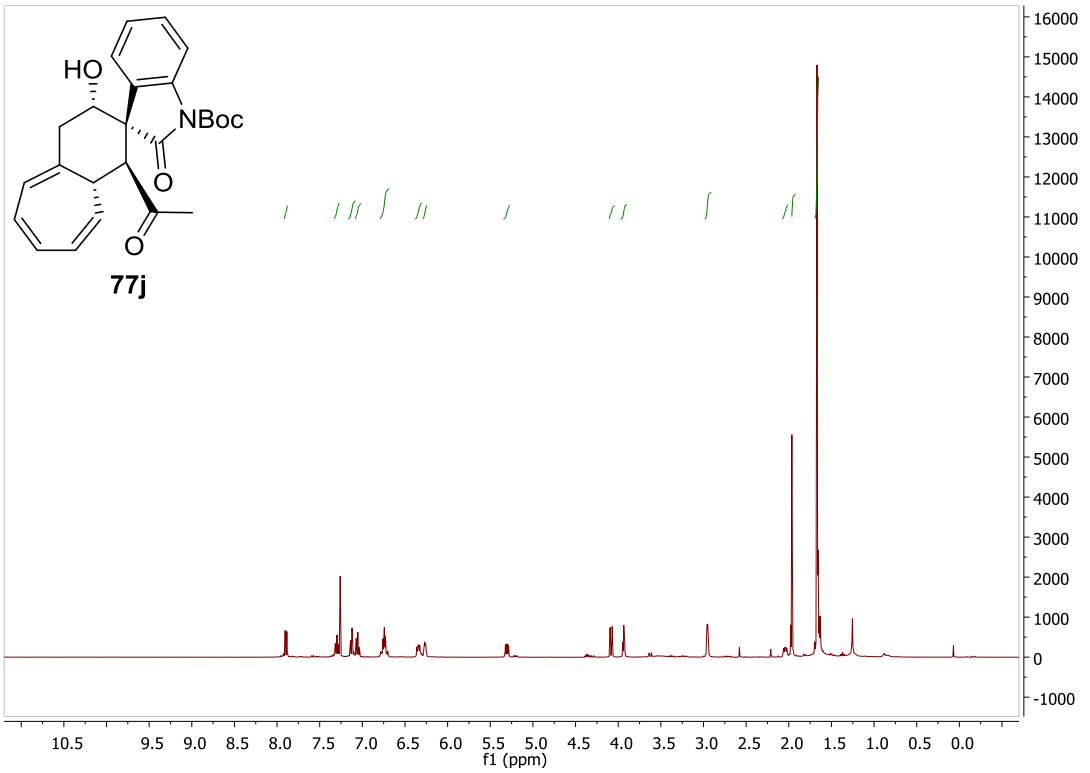
^{13}C NMR spectrum of **77h**



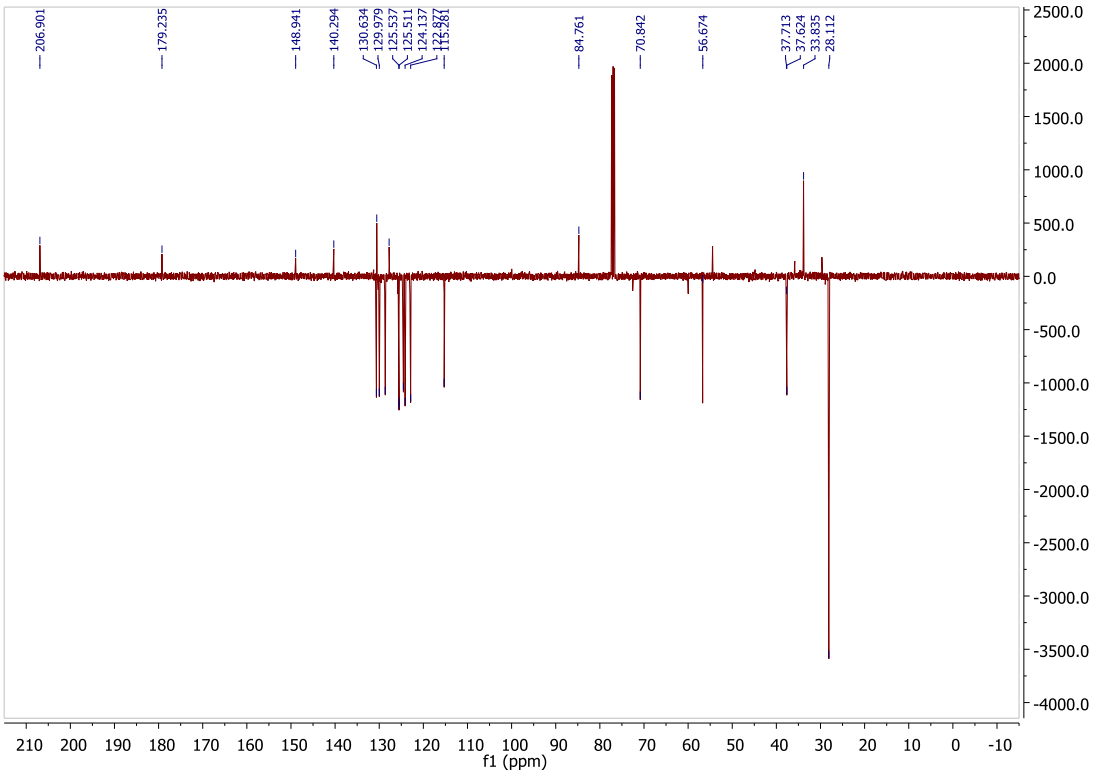
^{1}H NMR spectrum of **77i**



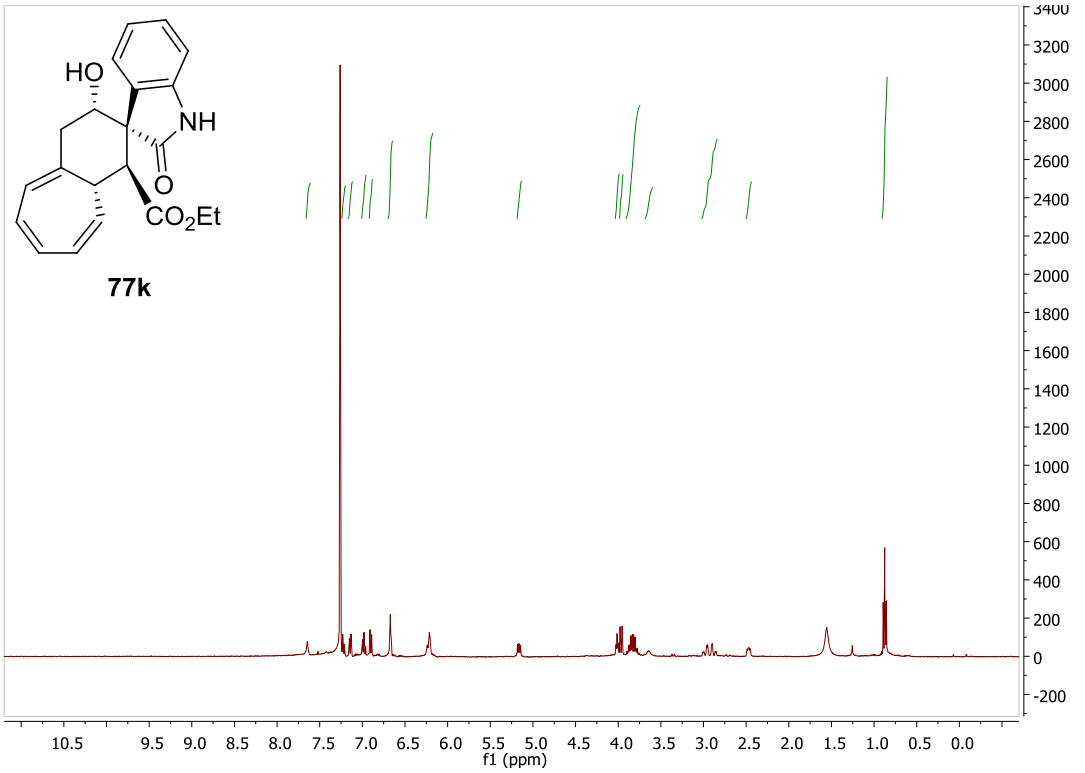
^{13}C NMR spectrum of **77i**



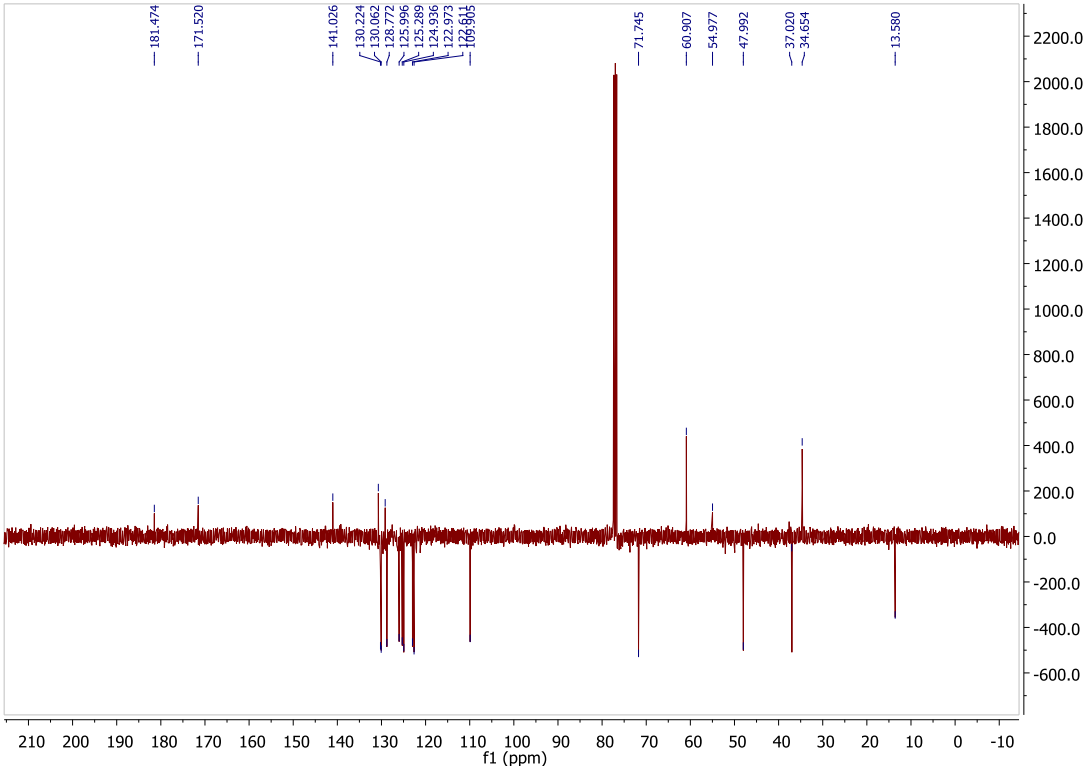
^{1}H NMR spectrum of **77j**



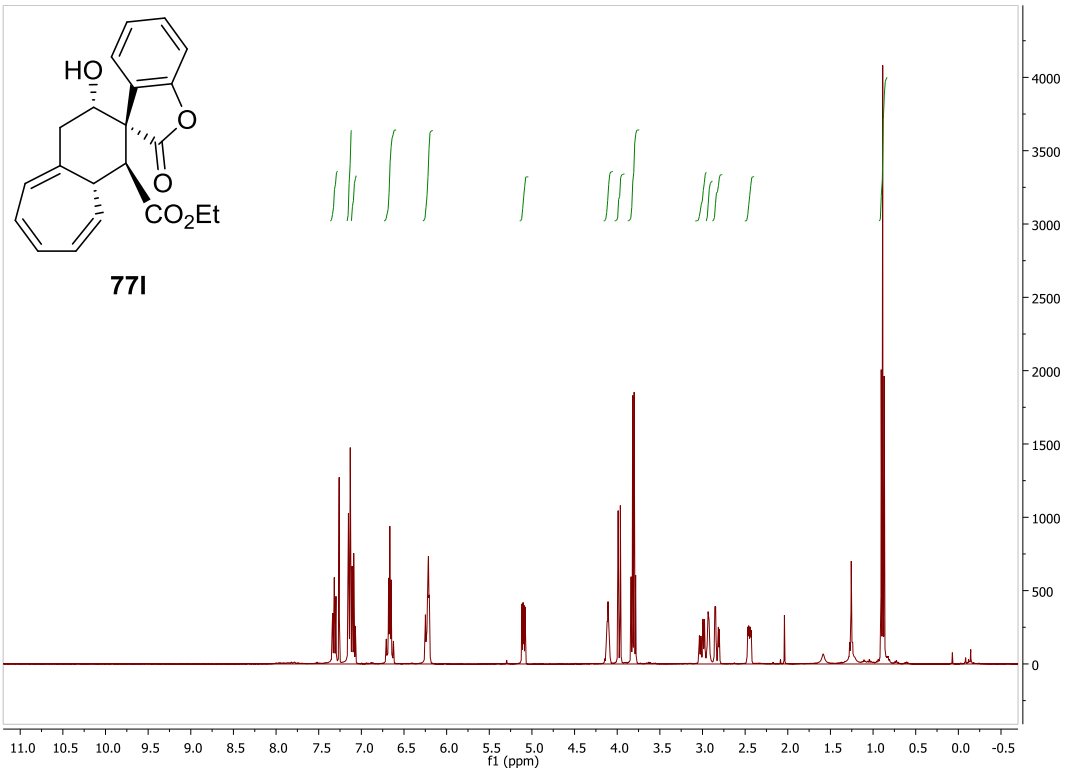
^{13}C NMR spectrum of **77j**



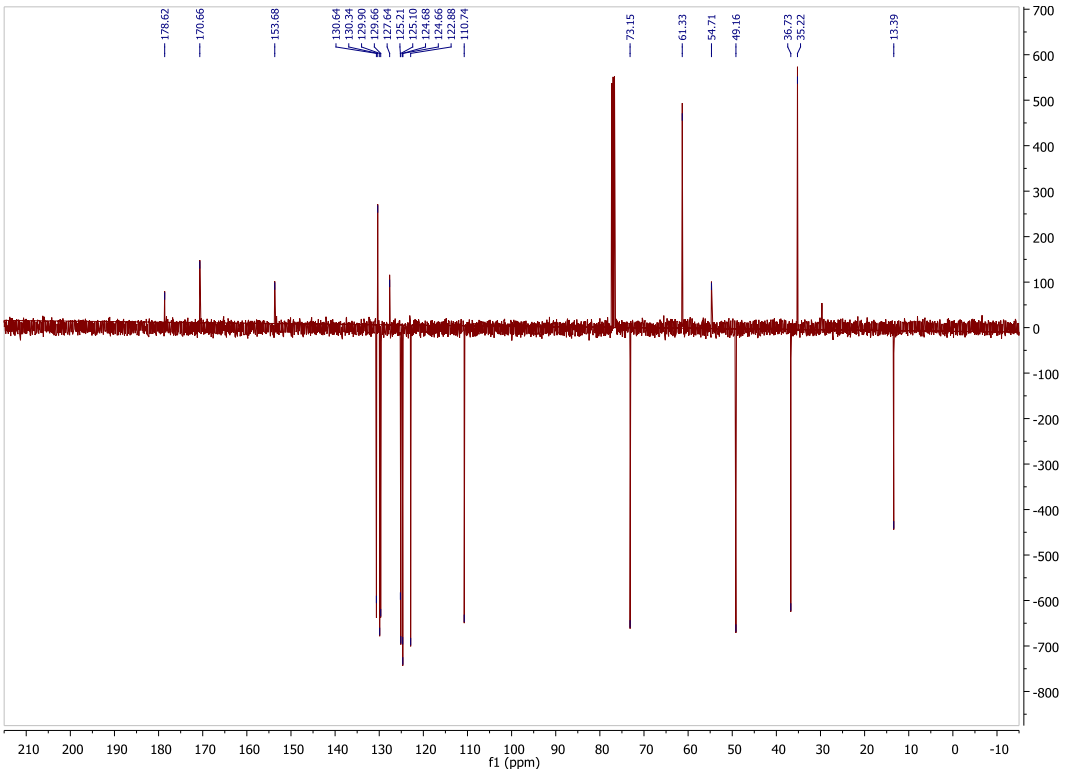
^{1}H NMR spectrum of **77k**



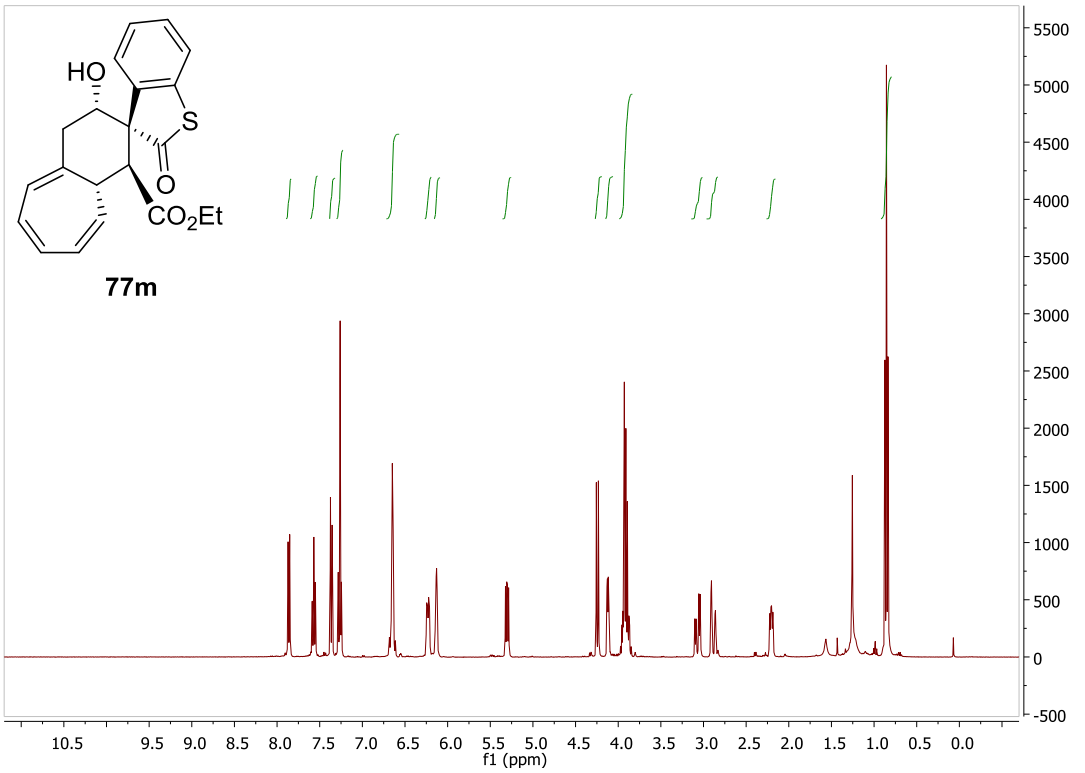
^{13}C NMR spectrum of **77k**



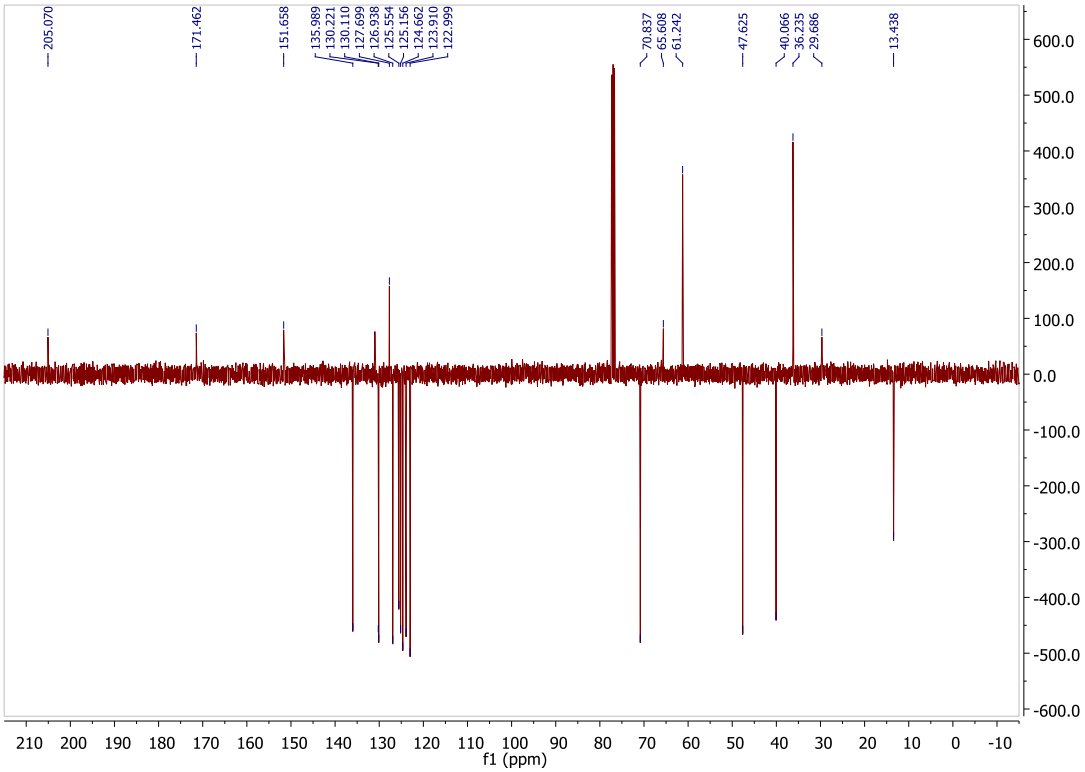
^{1}H NMR spectrum of **77l**



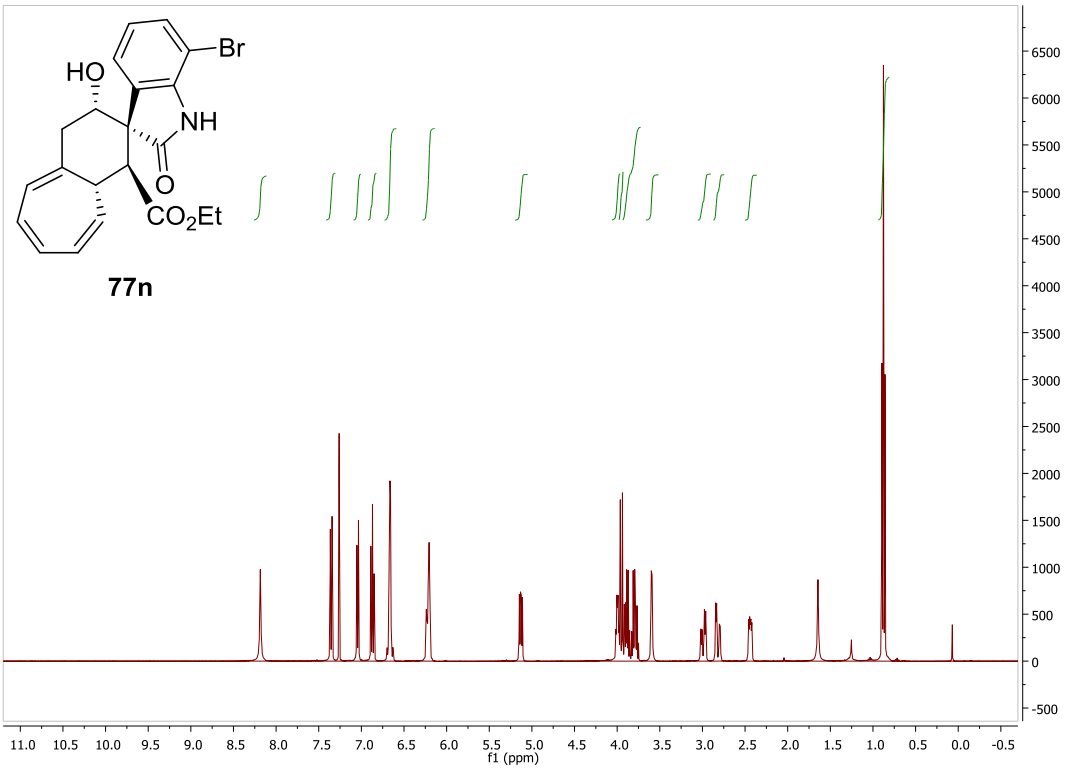
^{13}C NMR spectrum of **77l**



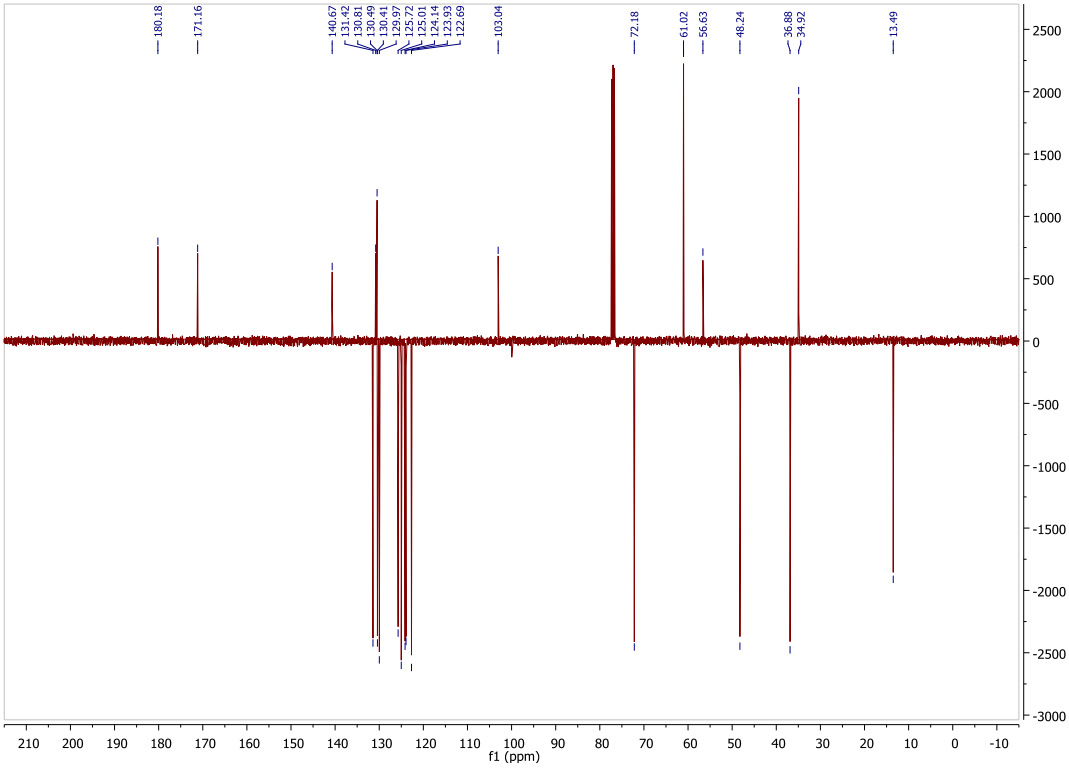
^{1}H NMR spectrum of **77m**



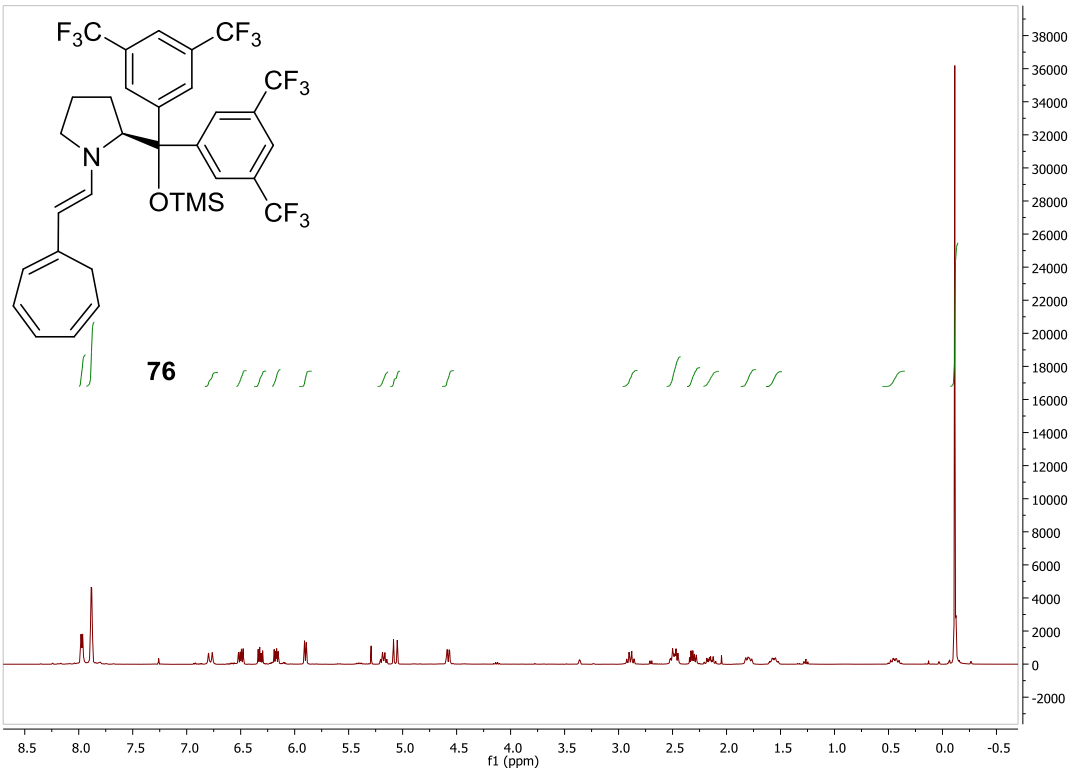
^{13}C NMR spectrum of **77m**



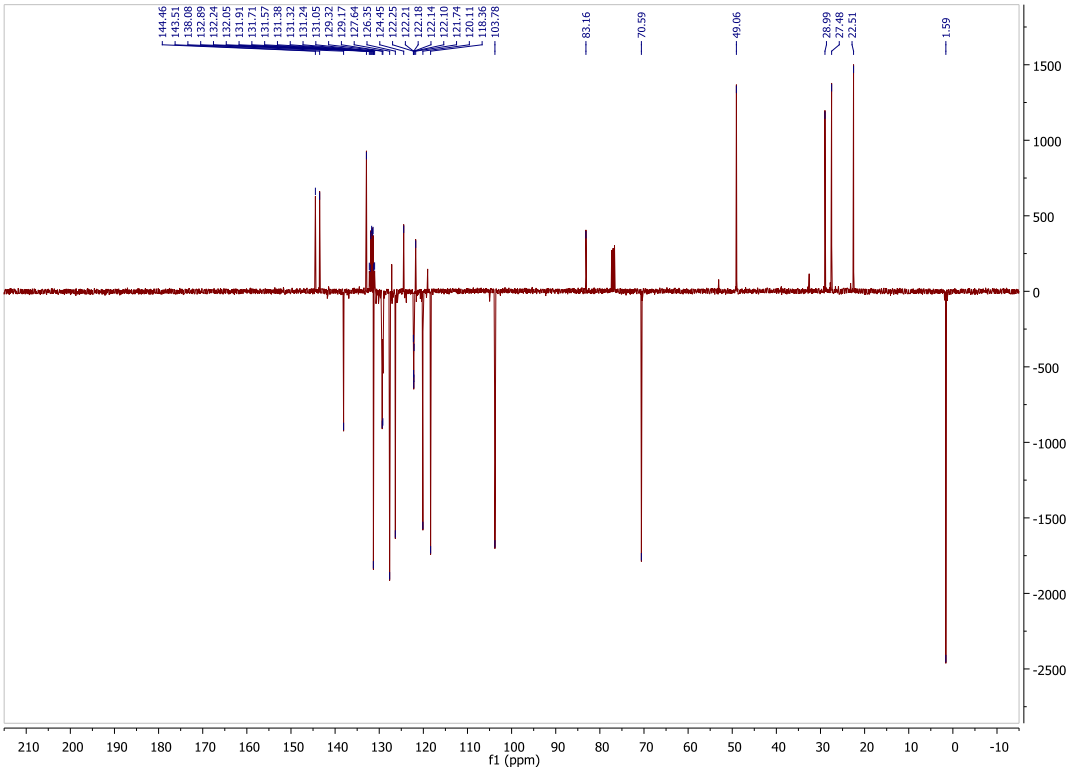
^{1}H NMR spectrum of **77n**



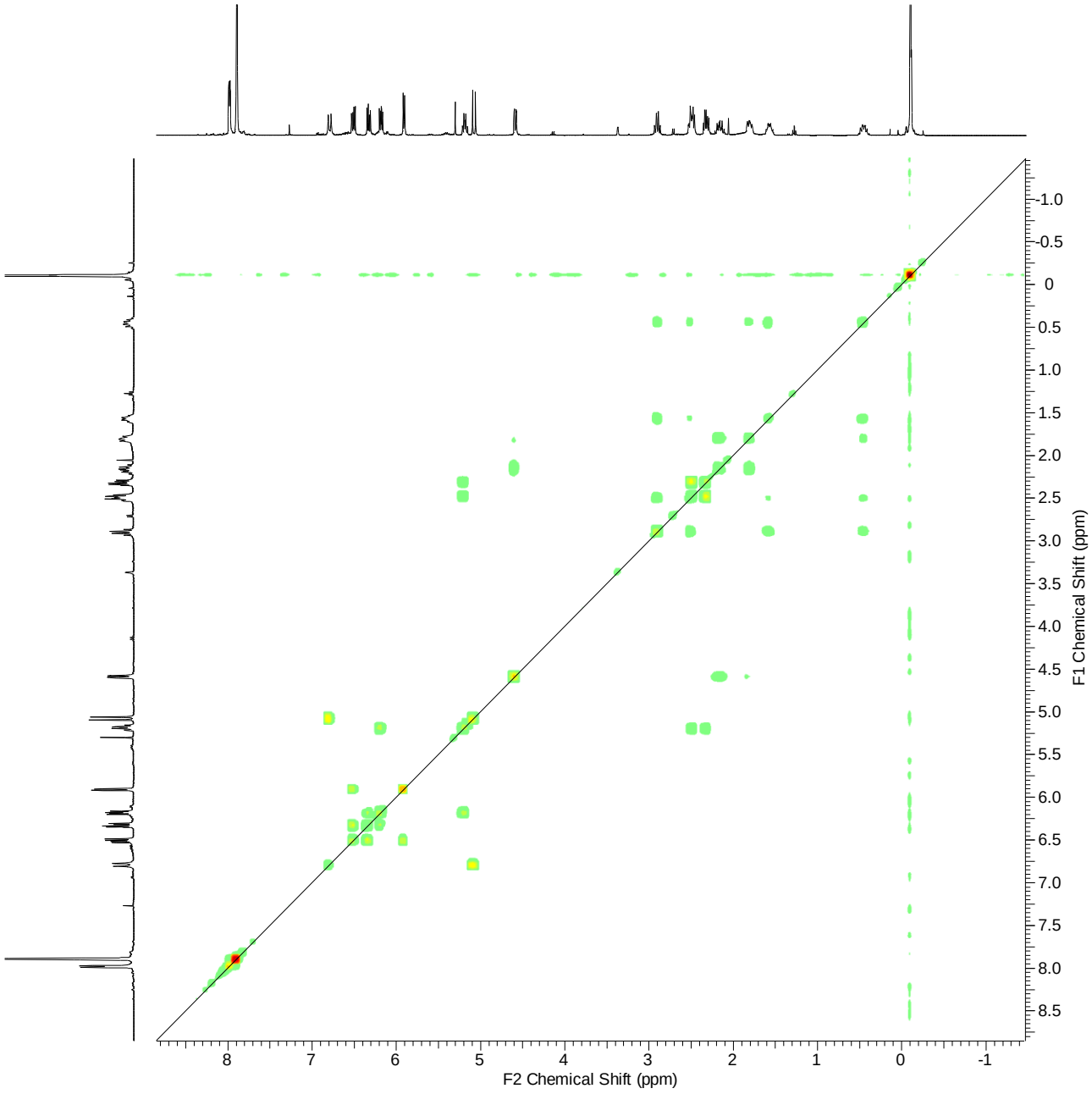
^{13}C NMR spectrum of **77n**



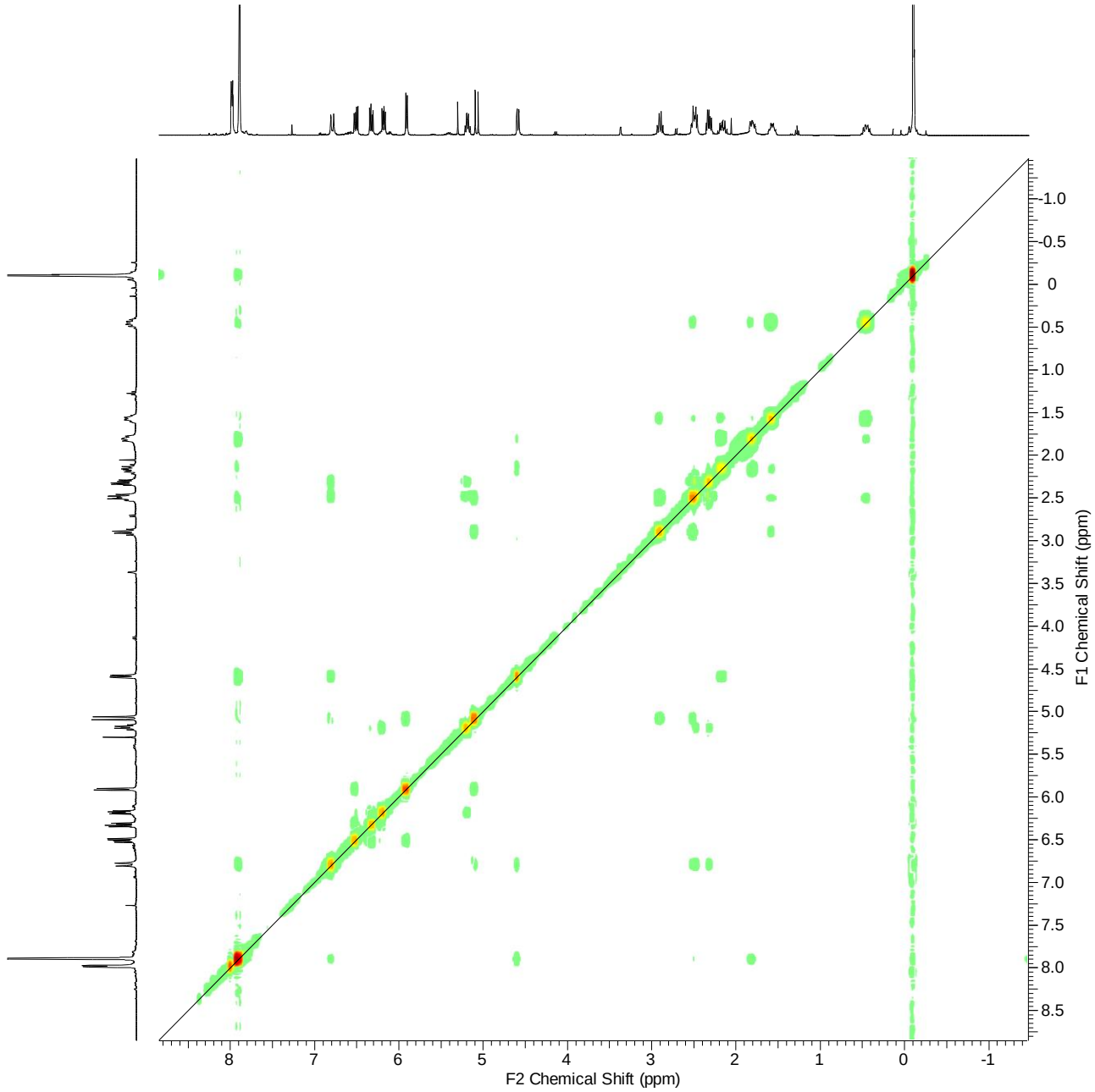
^{1}H NMR spectrum of **76**



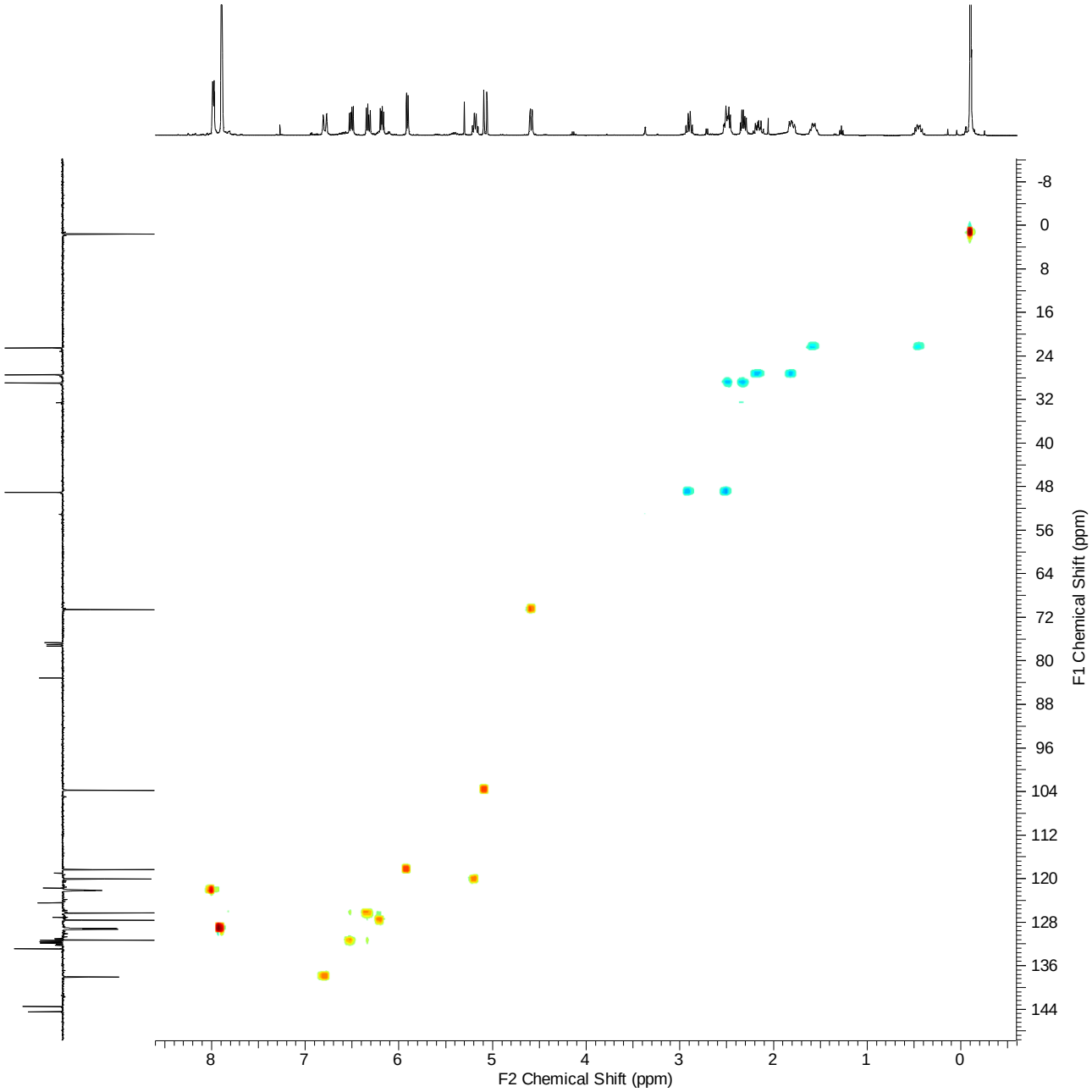
^{13}C NMR spectrum of **76**



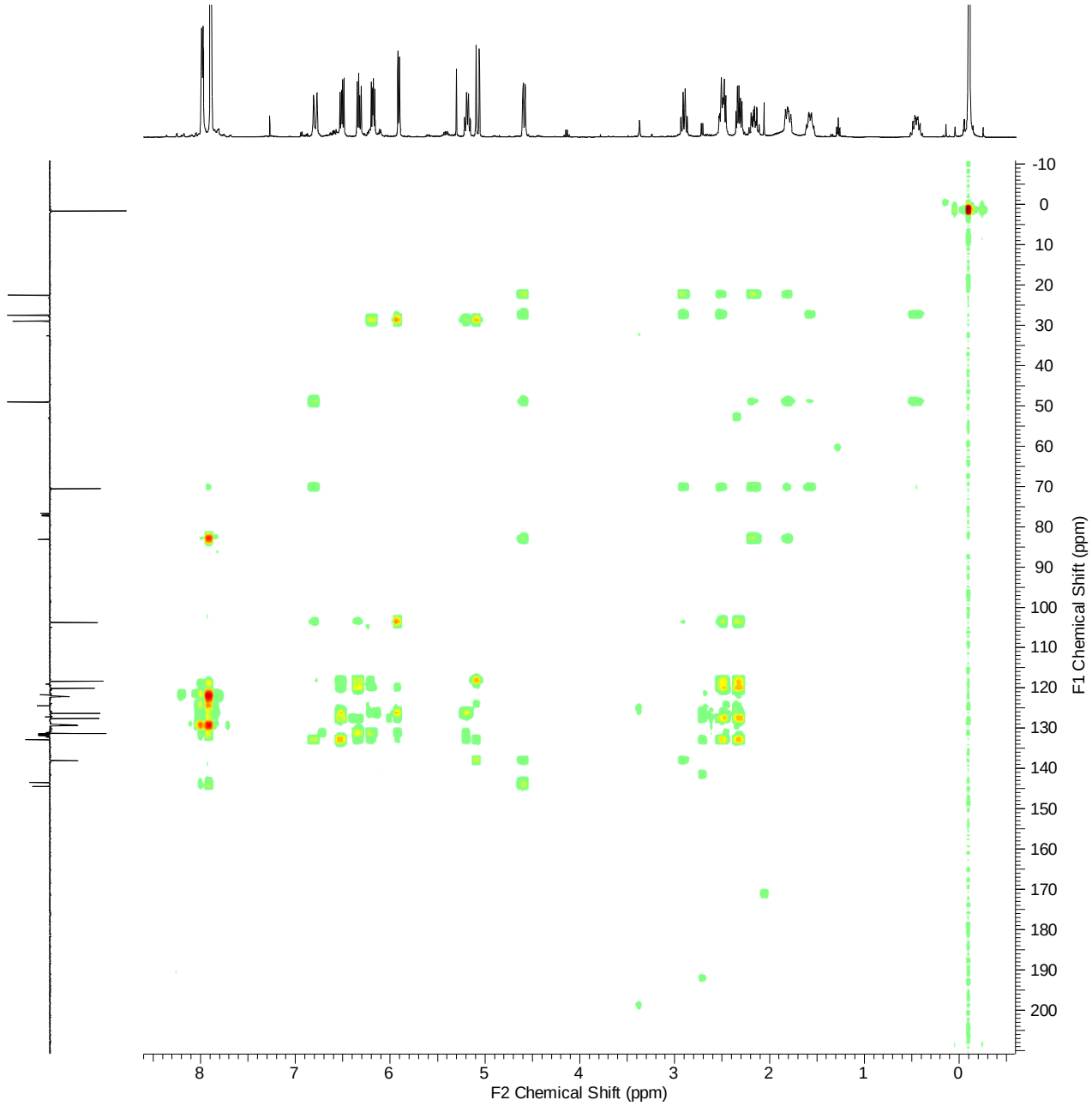
COSY NMR spectrum of **76**



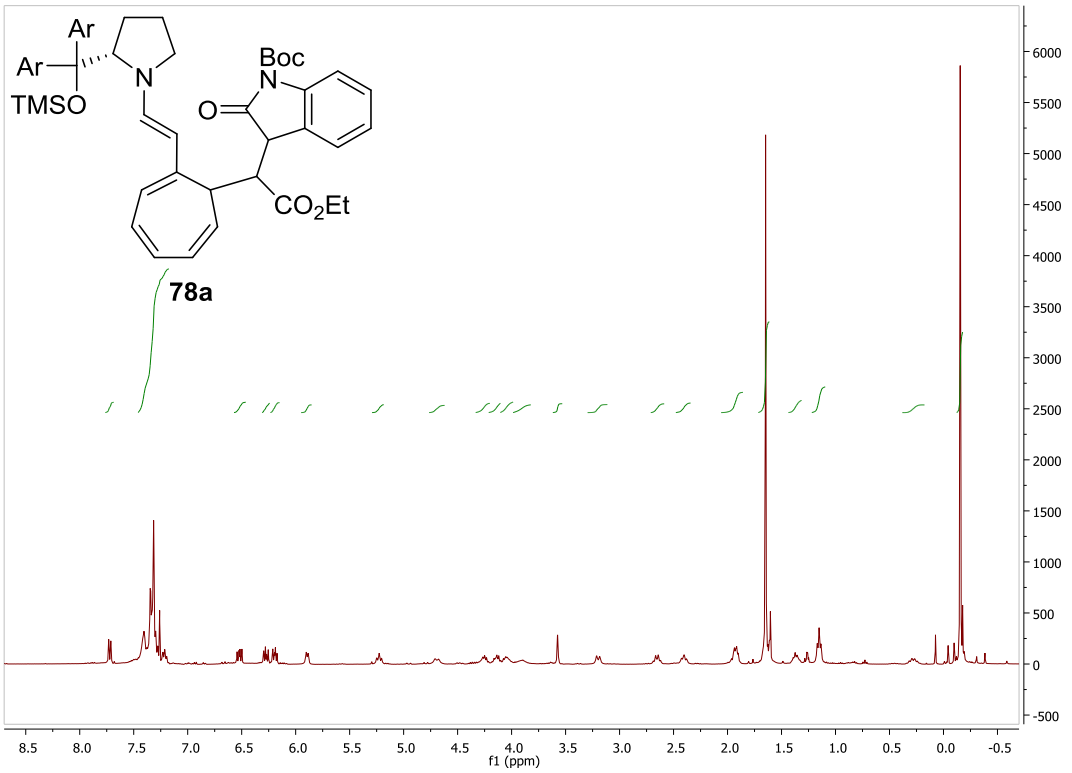
NOESY NMR spectrum of **76**



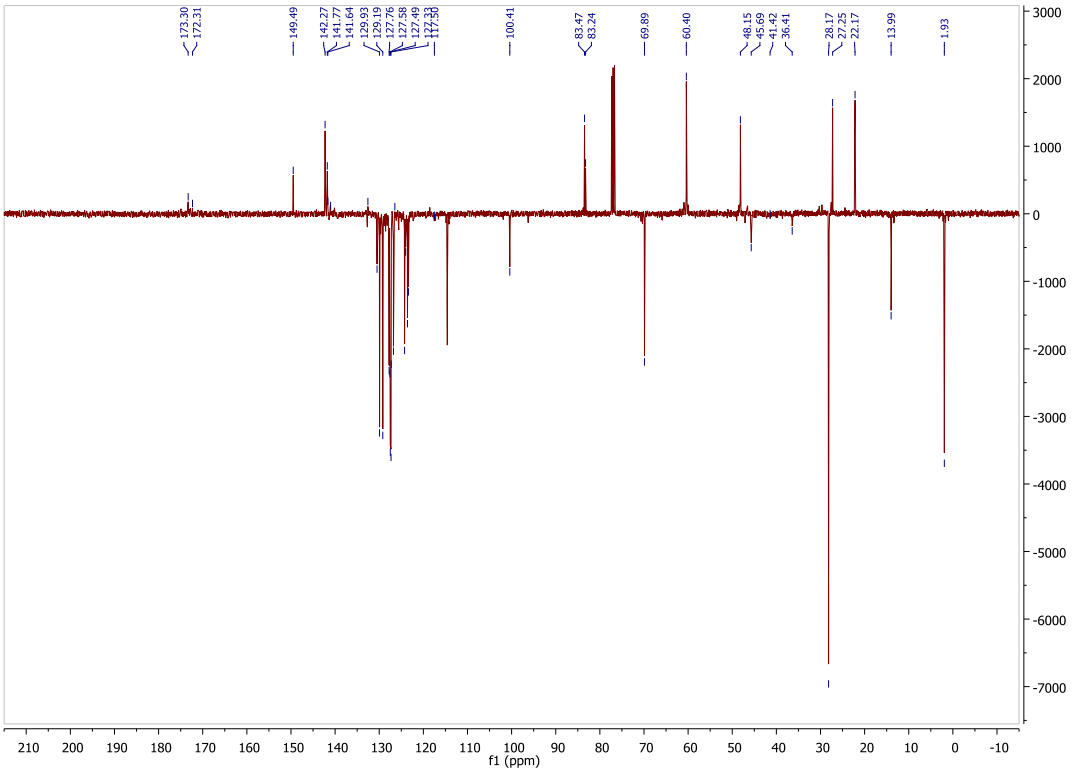
HSQC NMR spectrum of **76**



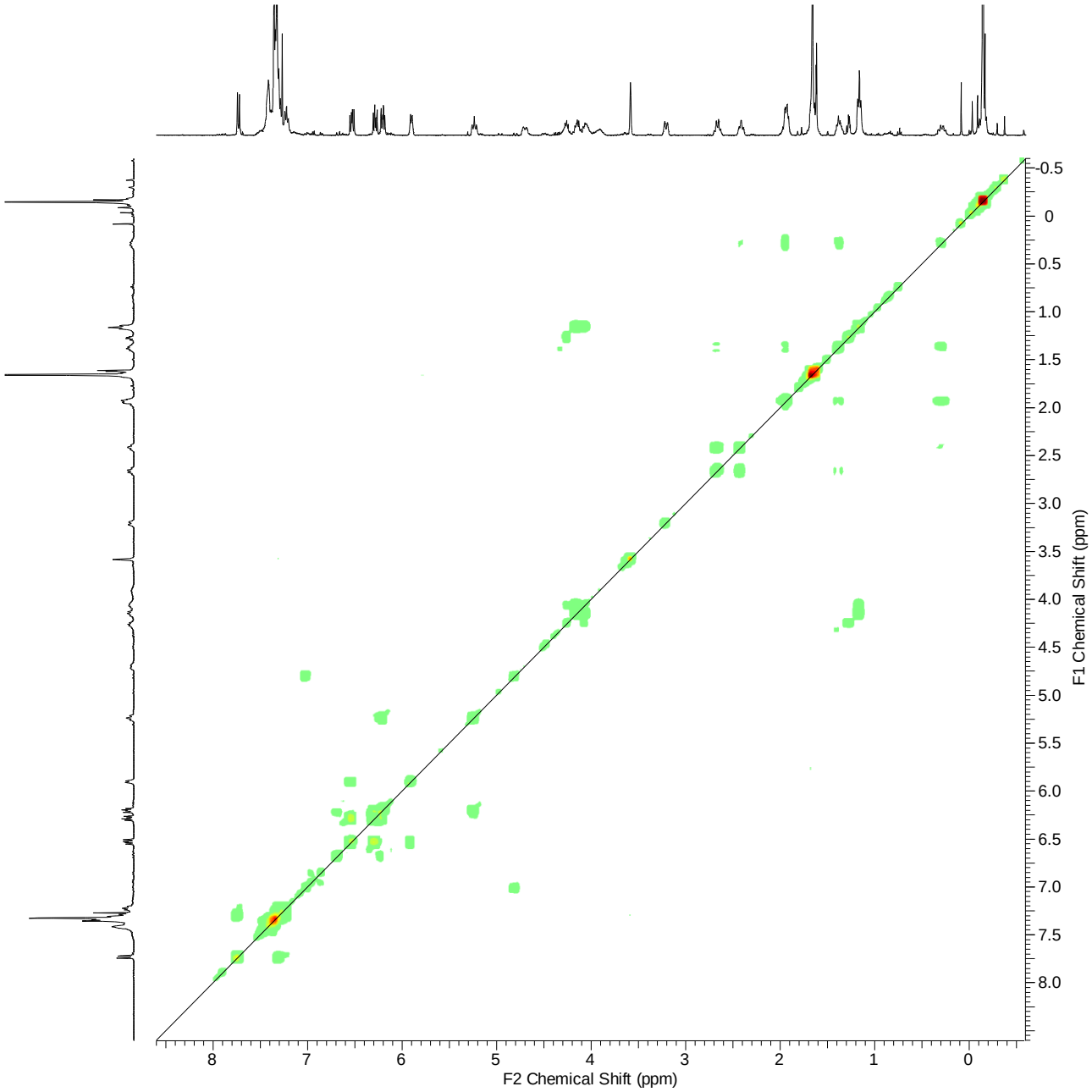
HMBC NMR spectrum of **76**



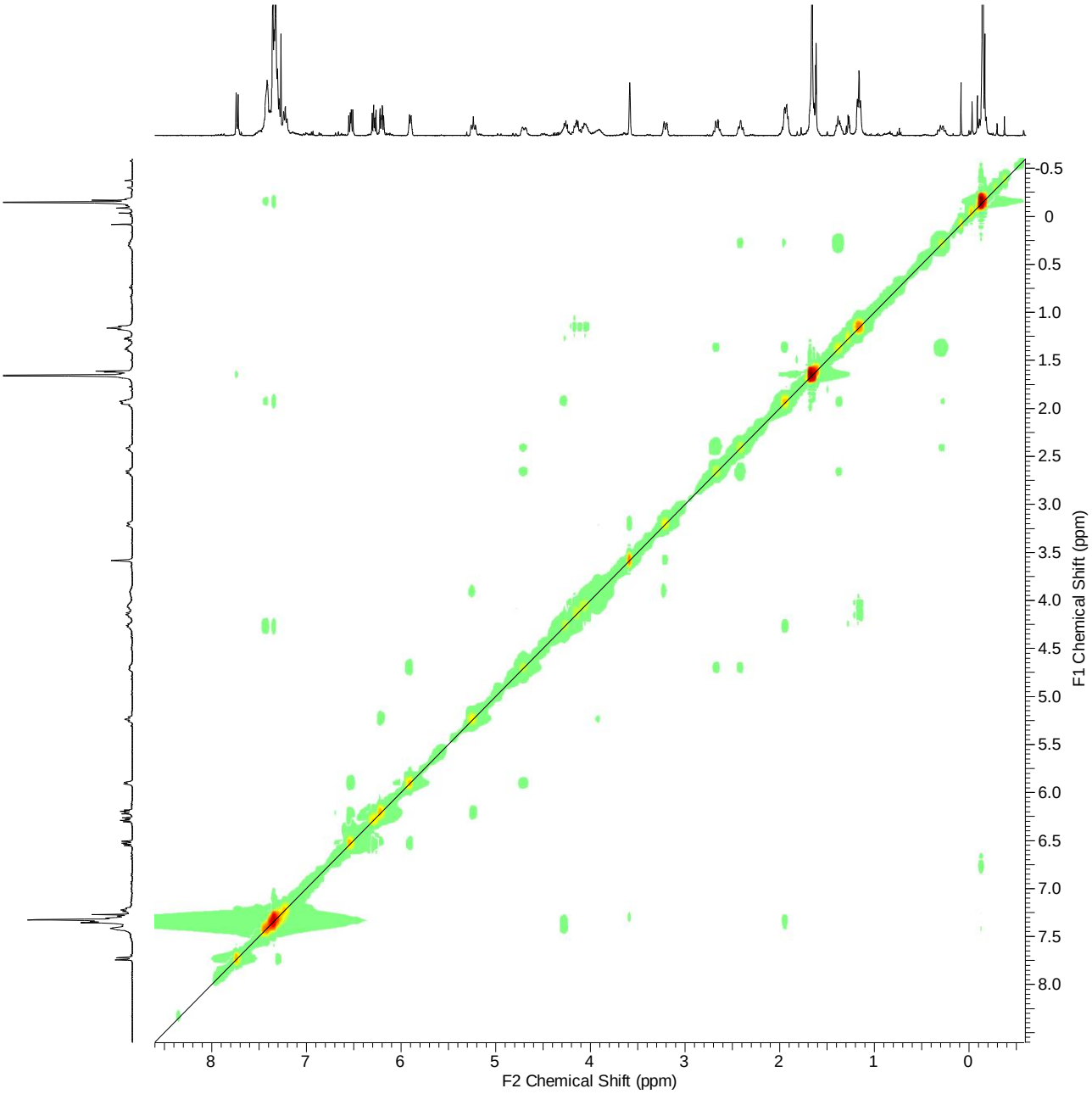
^{1}H NMR spectrum of **78a**



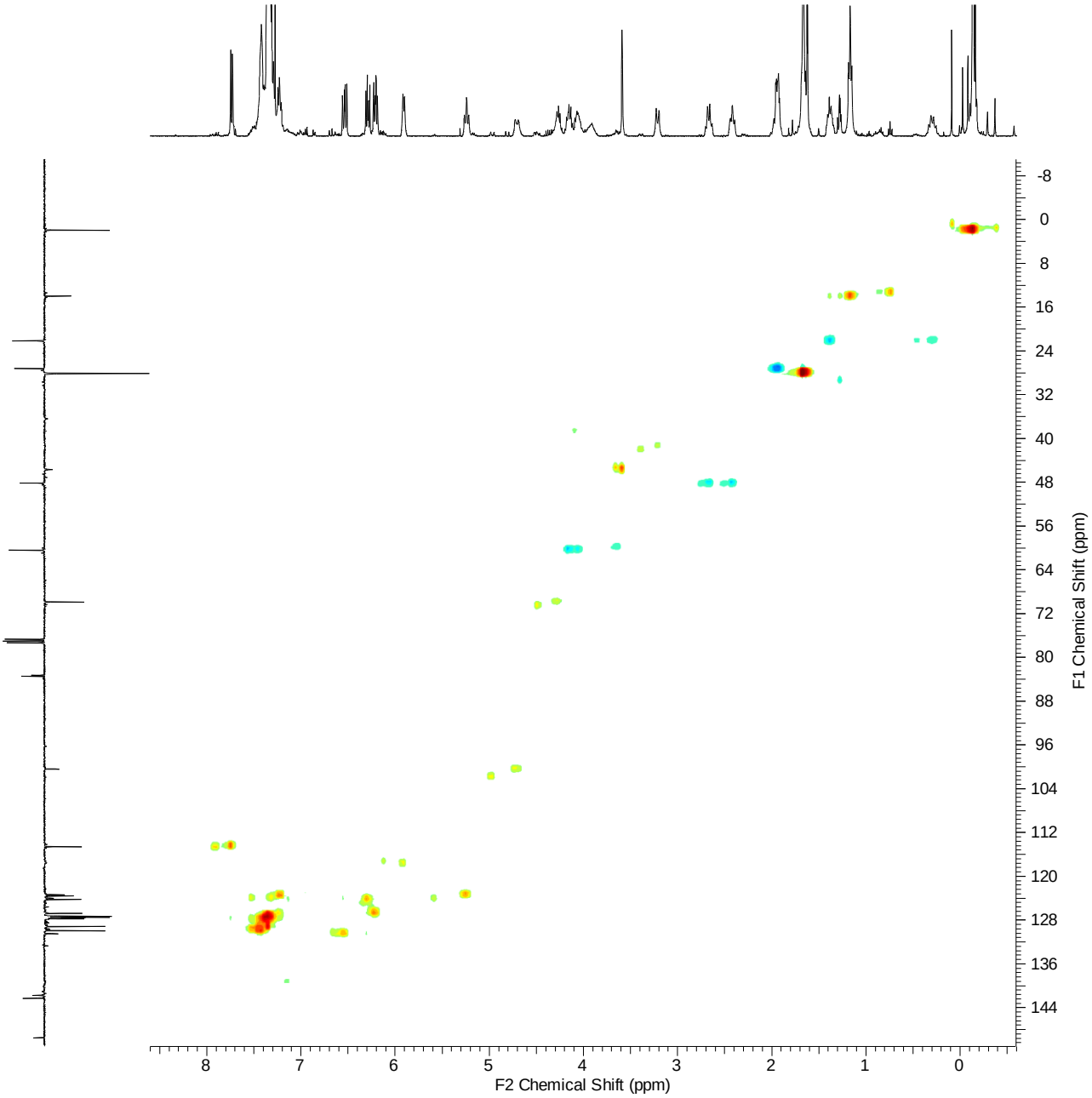
^{13}C NMR spectrum of **78a**



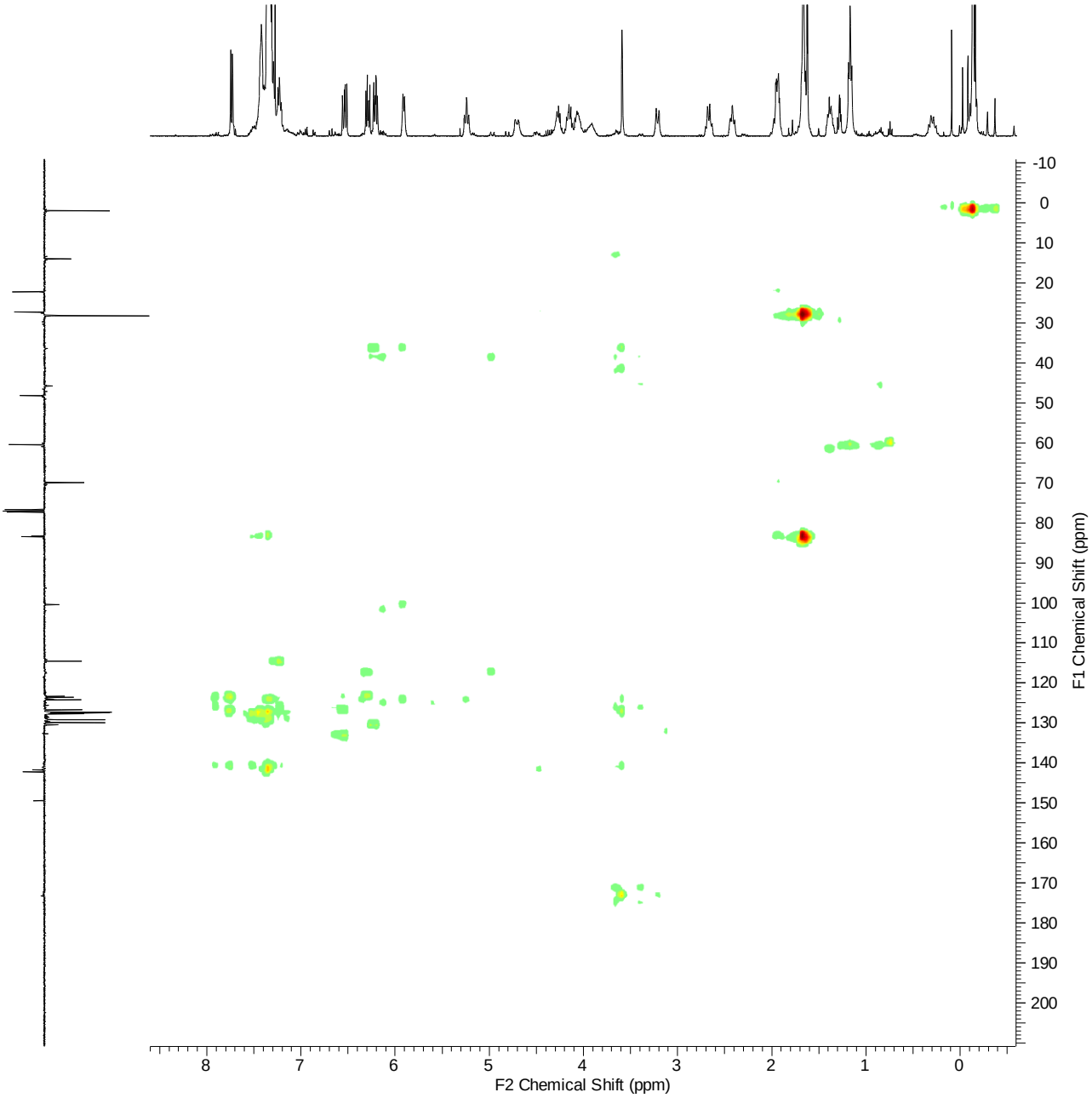
COSY NMR spectrum of **78a**



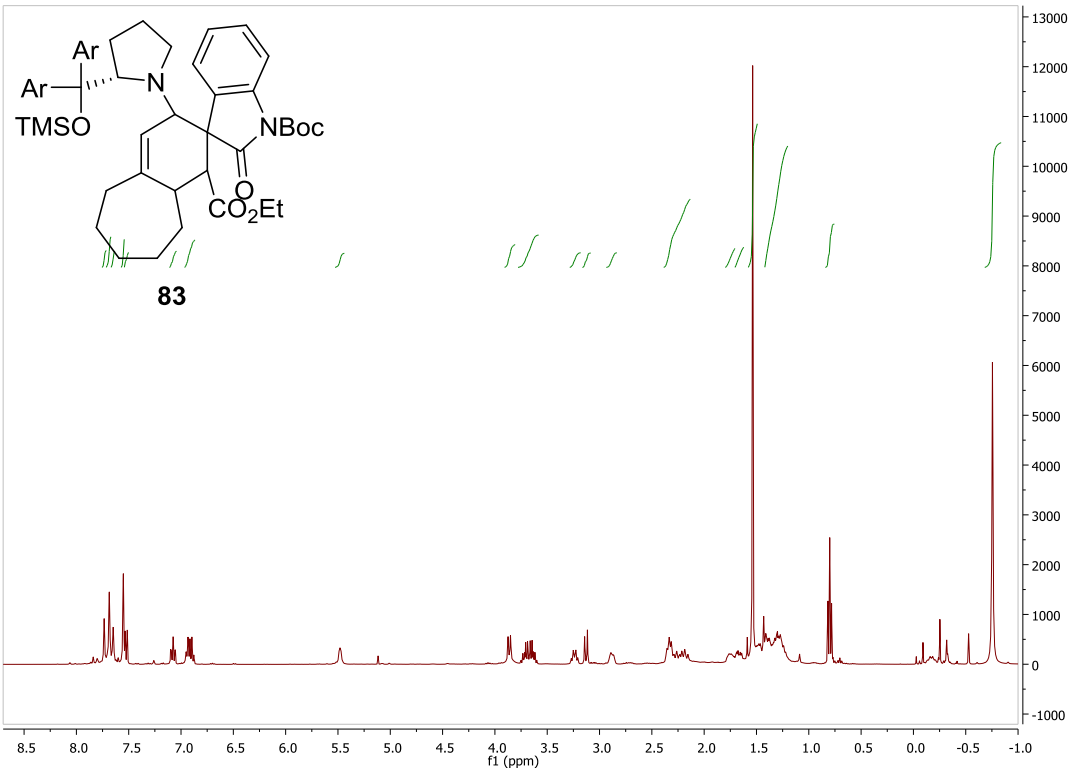
NOESY NMR spectrum of **78a**



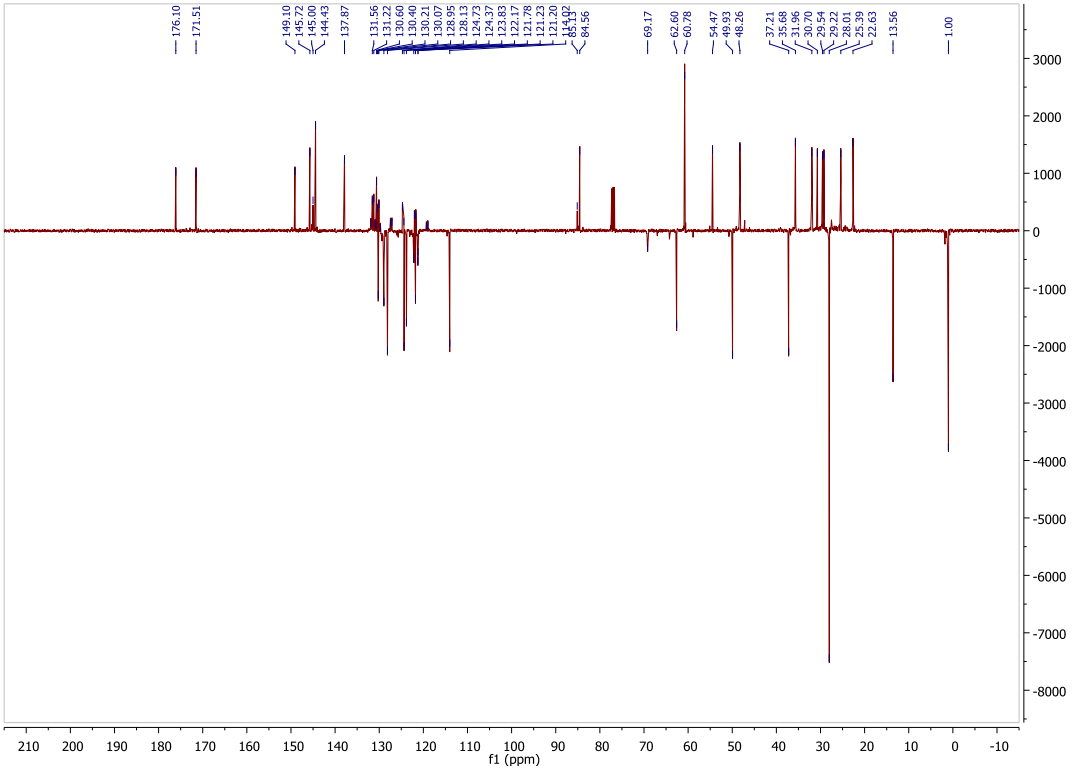
HSQC NMR spectrum of **78a**



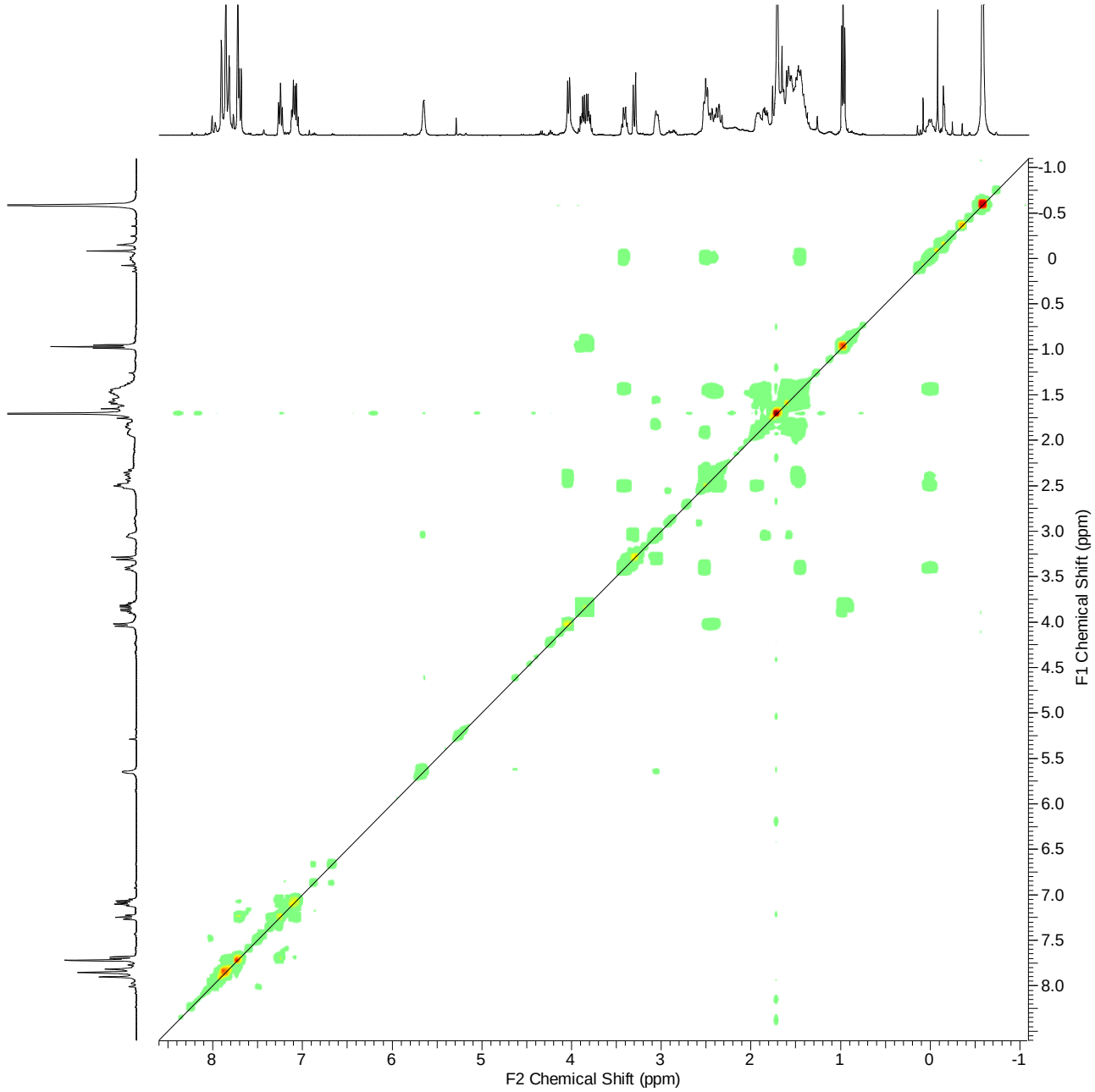
HMBC NMR spectrum of **78a**



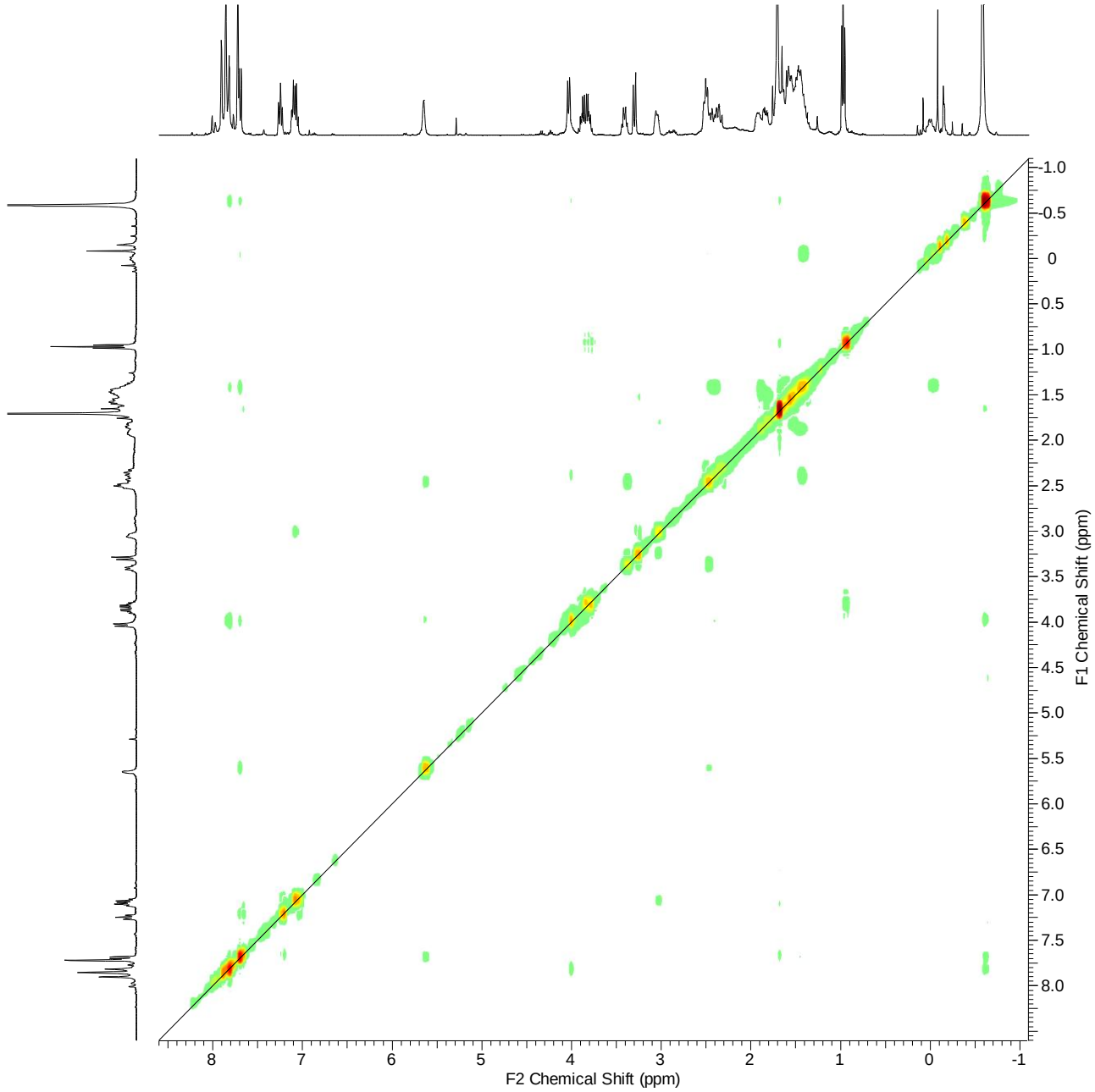
^{1}H NMR spectrum of **83**



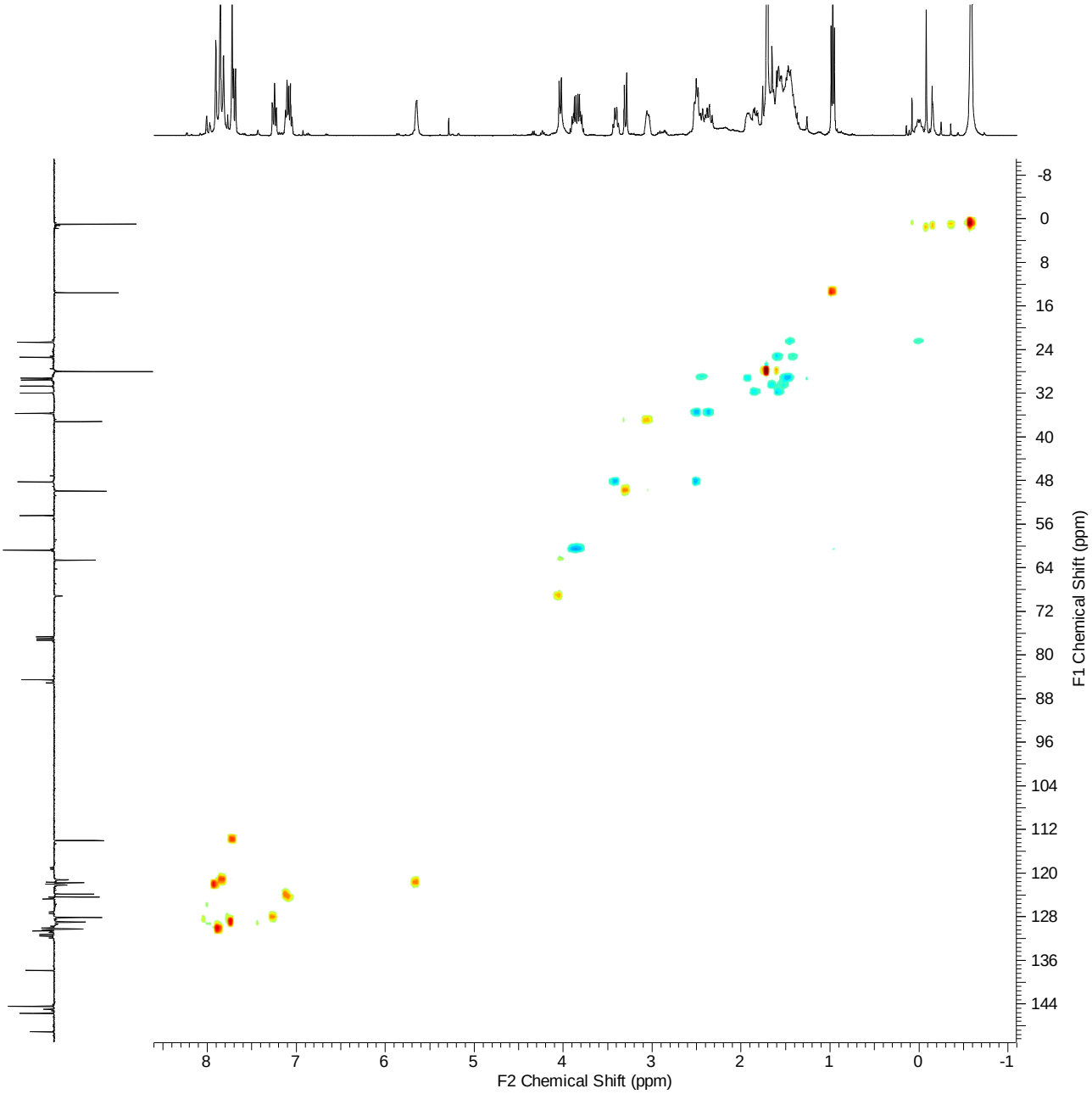
^{13}C NMR spectrum of **83**



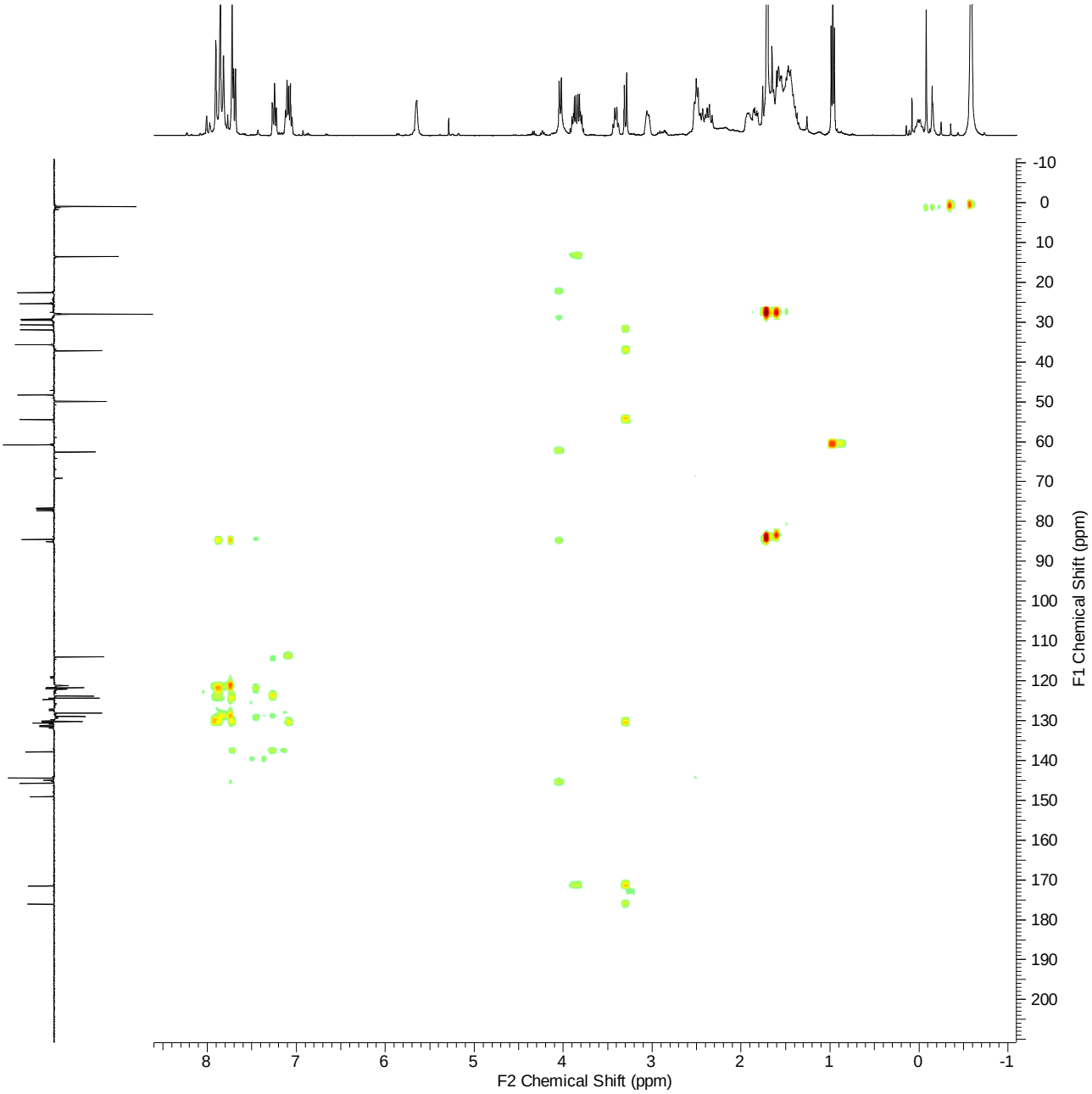
COSY NMR spectrum of **83**



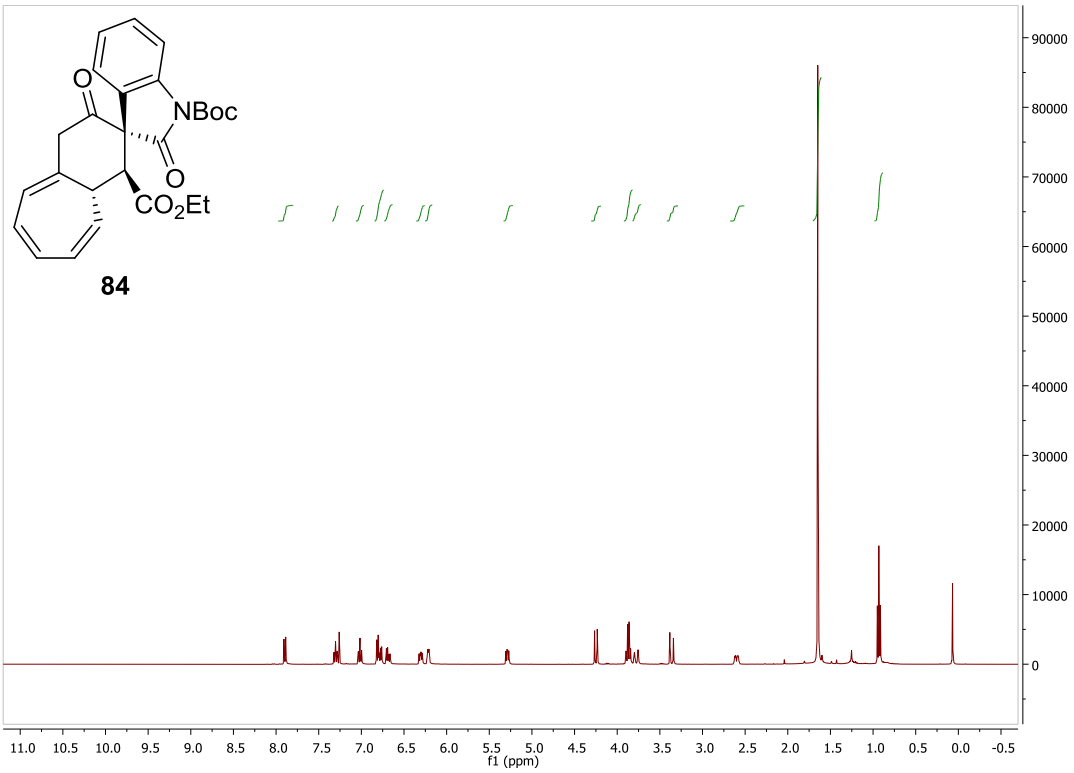
NOESY NMR spectrum of **83**



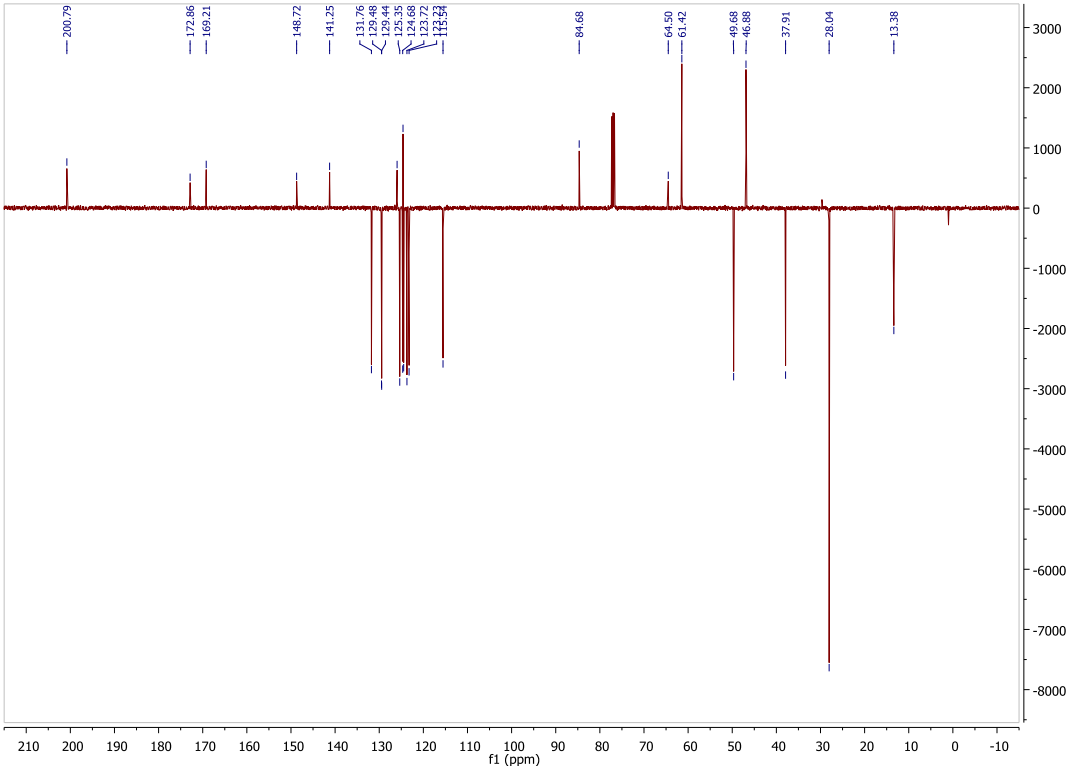
HSQC NMR spectrum of **83**



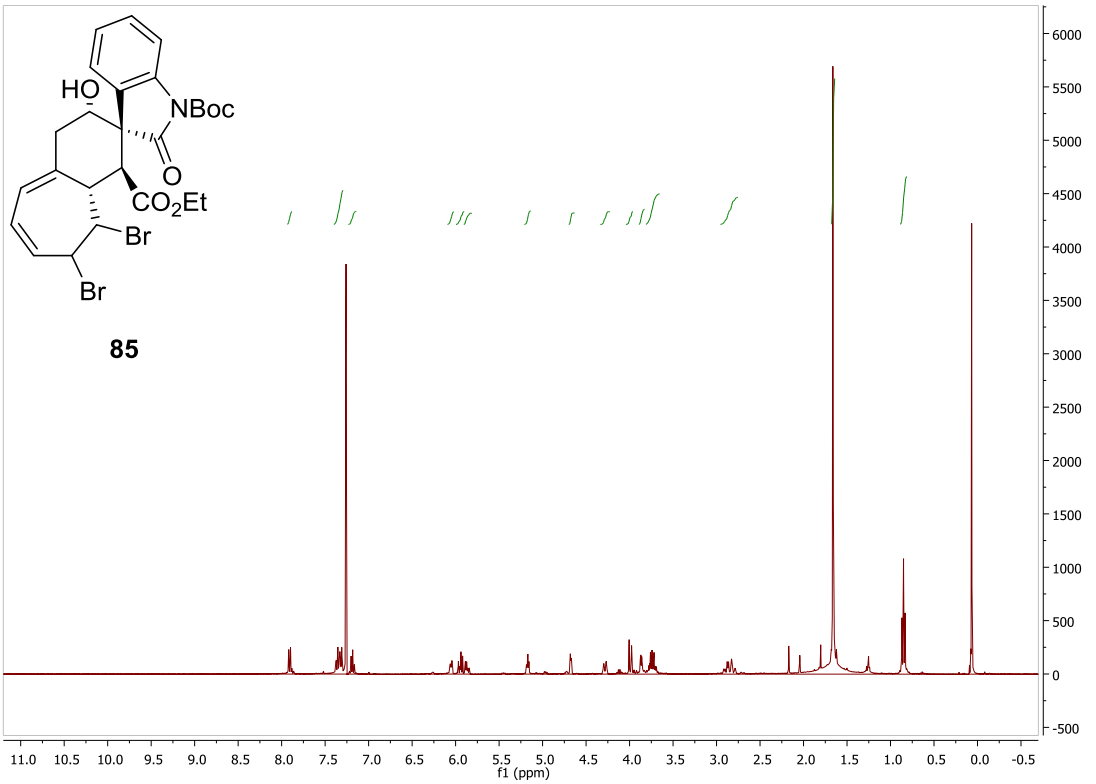
HMBC NMR spectrum of **83**



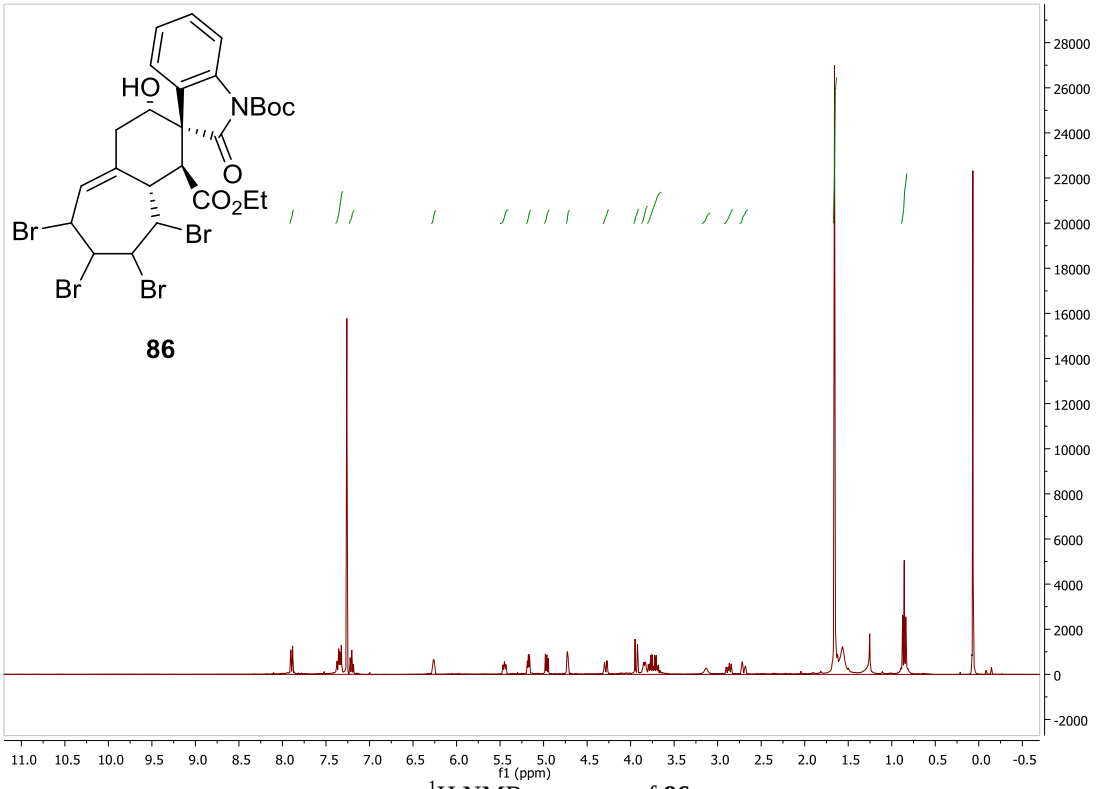
^{1}H NMR spectrum of **84**



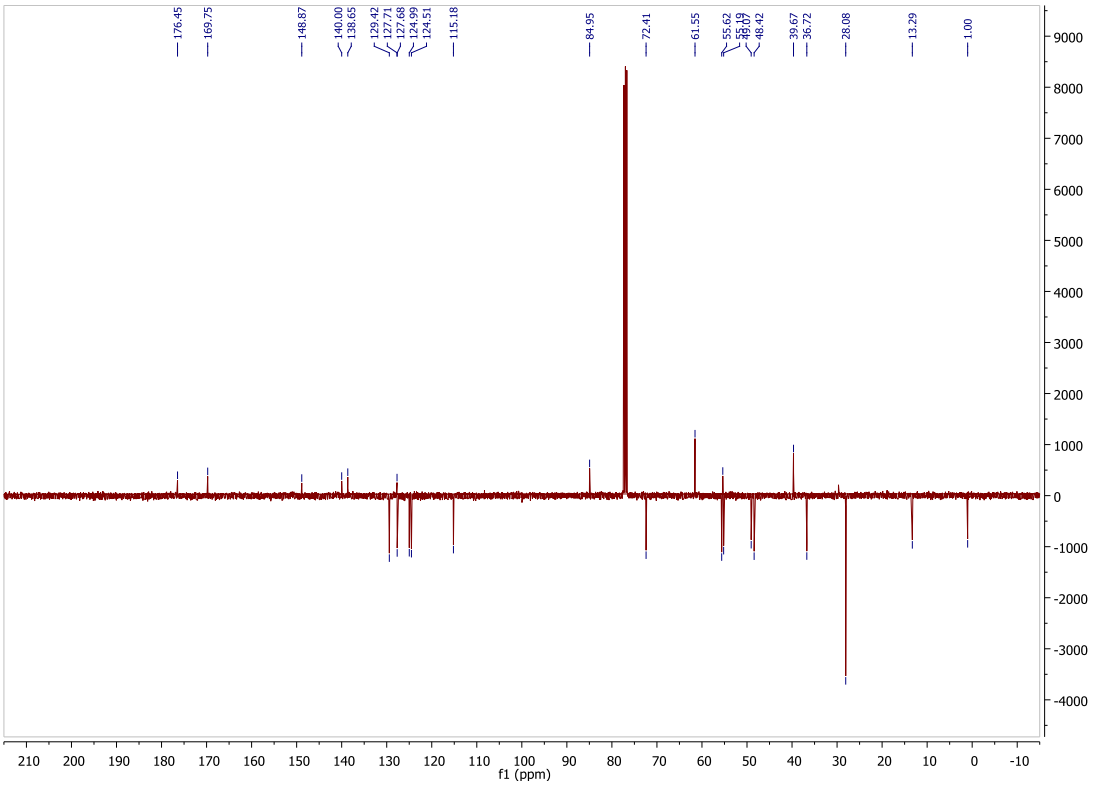
^{13}C NMR spectrum of **84**



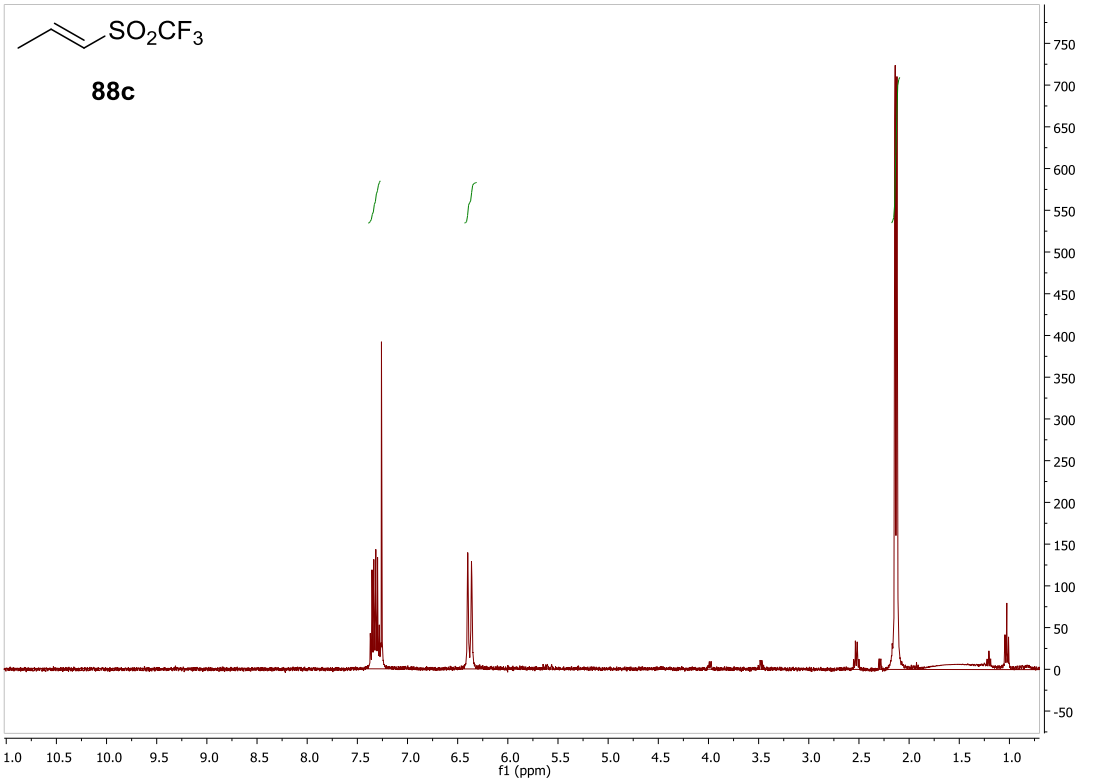
^{1}H NMR spectrum of **85**



^{1}H NMR spectrum of **86**



^{13}C NMR spectrum of **86**



^{1}H NMR spectrum of **88c**